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DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1956

ORIGINAL ARTICLES

GLOSSOPHARYNGEAL BREATHING AS AN AID TO RECOVERY FROM PARALYTIC POLIOMYELITIS*

By William D. Loeser, M.D.

ASSISTANT CHIEF, RESPIRATOR CENTER, CHRONIC DISEASE RESEARCH INSTITUTE, UNIVERSITY OF BUFFALO

(From the Respirator Center of the Chronic Disease Research Institute, University of Buffalo School of Medicine, Buffalo, New York)

Weakness of the respiratory muscles, so frequently encountered among the residuals of paralytic poliomyelitis, varies from a total paralysis of muscles of respiration to an imperceptible loss of this power. However, even with total paralysis of the respiratory muscles, certain patients have learned to maintain ventilation without the aid of mechanical devices by the use of glossopharyngeal breathing. This method of breathing is of greater importance than may be apparent from ventilation measurements since a significant psychological lift is provided when the patient realizes he is no longer entirely dependent upon respiratory aids for survival.

Glossopharyngeal breathing has long been known and used by swimmers to augment pulmonary filling prior to prolonged submersion. Such gulping efforts were first observed by Affeldt and Dail in a respirator center patient who developed the technique spontaneously[1-6]. This method has since proved to be of great value when used as a part of the program of weaning patients from mechanical devices.

Amphibians normally use glossopharyngeal breathing[7]; therefore, the name *frog breathing* is appropriate. The use of the valves in the larynx to trap air after each gulp and the passage of air over these valves during expiration may account for certain sounds, for example: the croak of the bullfrog. These valves are phylogenetically analogous to vocal cords. This is of interest since the vocal cords in humans are here used as valves, thereby simulating a more primitive function. Glossopharyngeal breathing differs from normal respirations which depend on negative intrapulmonic pressure to produce airflow into the lungs.

The present report presents our observations on the teaching of glossopharyngeal breathing to patients with respiratory paralysis. It has been our experience that with proper instruction it is possible to teach this mechanism

*From the University of Buffalo Respirator Center aided by an annual grant from the National Foundation for Infantile Paralysis.

to any cooperative patient. The time required to learn the process varies from 2 days to several months. Since it is a voluntary process, glossopharyngeal breathing cannot be used during sleep, and mechanical breathing aids must be used. As yet, we have observed no instance of a patient falling asleep spontaneously while gulping. There appears to be no danger that a patient would fall asleep and become asphyxic, inasmuch as restlessness and insomnia appear to be accompaniments of slight anoxia.

DESCRIPTION OF PROCESS. The process is performed in two steps. The mouth, tongue, soft palate and pharynx serve to force air toward the larynx. The soft palate is closed to prevent escape of air through the nose. After the gulping effort is made, the larynx is closed, holding the air in the lungs. The effort may be repeated several times, the vocal cords or larynx continuing to act as a valve allowing inflow of air, but preventing its escape. When the vocal cords are voluntarily opened, passive exhalation takes place quickly and the cycle is completed. Patients can be taught this method while still in chest respirators, the respirators being turned off for 30- to 60-second intervals while instruction and encouragement are given.

The patient is first taught to control expiration by closing the larynx toward the end of an expiration. This he may accomplish easily and silently. Or he may find it easier to master by first producing vocal sounds which then cease abruptly when closure of the larynx is achieved. The patient may check his proficiency at this stage by repeating the maneuver and resisting the exhalation produced by the chest shell.

The second step is taught while the patient's nose is held shut. He is told to force a mouthful of air down the throat and to resist the impulse to swallow. The instructor may then place a finger on the neck overlying the larynx to assist in directing closure of the larynx at the proper stage of the cycle. While the larynx is held closed, the next gulping effort is made. The force of the gulping effort must be great enough to overcome the partially closed glottis. The patient will soon learn to close the soft palate and obviate the use of a nose clamp.

Case Reports. CASE 1. M.C., a 24-year-old single white male, developed poliomyelitis with tetraplegia and respiratory paralysis which necessitated placement in a respirator. Tracheotomy was not required.

He was admitted to the Respirator Center 9 weeks after the onset. At the initial examination, the patient could breathe unassisted for intervals of 3 to 5 minutes. The tank respirator, cuirass respirator and rocking bed provided ventilatory support. There was marked muscle atrophy and absence of all deep tendon reflexes.

Three months after admission his unassisted breathing time was 15 minutes. Six months later this had increased to between one and 4½ hours daily. Some time during this interval, he had spontaneously begun to use glossopharyngeal respiration. He later recalled that he had known and used this process prior to his illness, over-inflating his chest to increase breath-holding time while swimming. Unassisted breathing time varied between 3 and 7 hours, using this method. He alternated between regular and glossopharyngeal breathing. In the fourteenth month, his unassisted time averaged about 7 hours daily with a maximum of 12. Values obtained with the spirometer are recorded in Table 1 and in Fig. 1.

CASE 2. S.V., an 18-year-old girl student, developed acute bulbar spinal poliomyelitis with rapid onset of tetraplegia. Development of dysphagia necessitated a tracheotomy. Following the acute illness, she needed constant artificial respiration and had almost complete motor loss except for some motion of the fingers and toes. On admission to the Respirator Center, 129 days after onset, she could tolerate only 30 seconds out of the tank respirator. The only visible respiratory efforts were with the neck muscles. A roentgenogram of the chest showed bullous emphysematous areas.

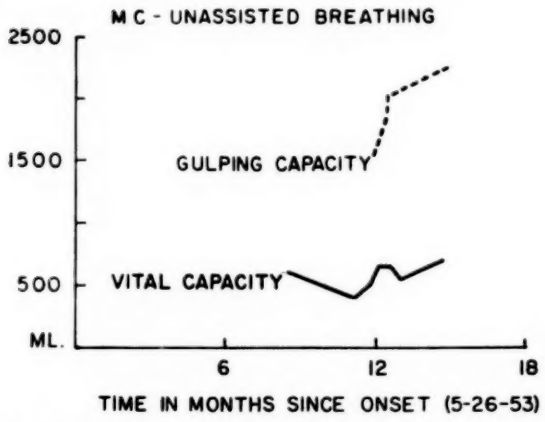

Fig. 1.—Vital capacity measurements on patient M.C. are compared with the capacity of the chest when glossopharyngeal breathing is used. Although the vital capacity rarely exceeded 600 ml., this man was able to show a capacity exceeding 2000 ml. with the aid of glossopharyngeal breathing.

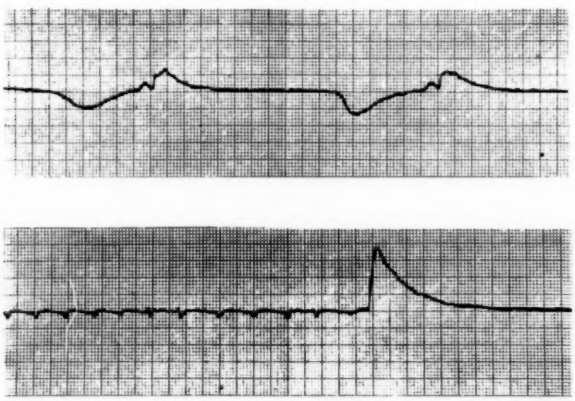

Fig. 2.—Two pneumotachograms are shown for comparison of the force of cough of patient S.V. In the upper figure, two inspiratory efforts are shown each followed by a cough. Peak rates of flow were about 1 L. per second. In the lower figure, 12 gulping efforts are shown followed by a cough. Note that the peak rate of flow is approximately 4 times the flow in the top figure.

TABLE 1.—DATA ON EFFICIENCY OF UNASSISTED AND GLOSSOPHARYNGEAL BREATHING IN CASE 1.

M.C., June 19, 1954

	Min. O_2 Uptake L.	*Min. Ventil. L.*	*Ventil. Quotient %*	*Tidal Volume L.*	*Respirations Per Min.*	*Vital Capacity L.*
Unassisted breathing	0.25	7.7	3.3	0.48	16	0.6
Glossopharyngeal breathing	—	—	—	—	5	2.0

Initial progress of "weaning" from respiratory aids was slow. One month after admission she was fitted with a cuirass respirator, and 7 months later was started on the rocking bed. After 6 months she was able to breathe unassisted for only 15 to 30 minutes. The tracheotomy tube was removed in the tenth month.

One year after admission, she breathed unassisted for one hour daily but with urging extended the time on one occasion to 4 hours. She used the rocking bed several hours daily.

TABLE 2.—DATA ON EFFICIENCY OF UNASSISTED AND GLOSSOPHARYNGEAL BREATHING IN CASE 2.

S.V., August 6, 1954

	Min. O_2 Uptake L.	*Min. Ventil.* L.	*Ventil. Quotient* %	*Tidal Volume* L.	*Respirations Per Min.*	*Vital Capacity* L.
Unassisted breathing	0.22	5.17	4.3	0.25	20.5	0.3
Unassisted breathing + 4 gulping efforts	0.22	3.5	6.4	0.29	12.0	"gulping vital capacity" 0.9

TABLE 3.—DATA ON EFFICIENCY OF UNASSISTED AND GLOSSOPHARYNGEAL BREATHING IN CASE 3.

C.A., July 19, 1954

	Alveolar CO_2	*Alveolar O_2*	*Tidal Vol.* L.	*Respirations Per Min.*	*Vital Cap.* L.	*Min. Ventil.* L.	*Effective Min. Ven.* L.
Inspiration alone			0.46	17	0.46	7.8	5.2
Gulping alone			—	—	2.4	—	
Combined	5.2%	105 mm.	0.54	12.5	—	6.7	4.8

Her vital capacity was 0.25 L. and minute ventilation was 5 L., approximately 15 months after the onset.

Twenty months after the onset an effort was made to teach this patient glossopharyngeal breathing. After a single period of instruction, she was able to demonstrate glossopharyngeal breathing with surprising agility. With the assistance of this method of respiration, her gulping vital capacity increased sharply to 0.65 L. Two weeks later, vital capacity was 0.4 L. but the gulping vital capacity was 0.9 L., increasing further to 1.1 L. shortly thereafter. See Fig. 2 and Table 2.

CASE 3. Three days after C.A., a 31-year-old farmer, developed poliomyelitis with tetraplegia, his vital capacity had fallen from 2.5 to 0.6 L. A tracheotomy was performed and he was placed in a tank respirator.

Ninety-two days after onset, he was admitted to the University of Buffalo Chronic Disease Research Institute. The respiratory rate in the tank respirator, upon which he was completely dependent, was 20 per minute. Vital capacity was 0.2 L. Within 12 days he tolerated a cuirass respirator, used the rocking bed for one to 4 hours, and breathed unassisted up to 10 minutes. During the first month he acquired the ability to "gulp" by observing another patient. On his 45th day, vital capacity was measured at 0.3 L.; with the aid of gulping it was 0.8 L. By this means he extended his unassisted breathing time to 30 minutes. This was further extended to one hour at one month, and 4 to 5 hours after 2 months. The respiratory rate was 13 per minute using the combined breathing method; the rate was 18 per minute when he ventilated without gulping.

A spirometric record of his respiration is presented 10 months after admission (Fig. 3). Additional records of respiration were recorded first, inspiration alone, then gulping alone and finally combined gulping and inspiration (see Table 3). When the patient used the combination of inspiratory effort followed by two gulping efforts and then expiration, an efficient rate of 12.5 per minute and a tidal volume of 0.54 L. was produced. A decrease in minute ventilation is noted in contrast with that obtained by respiration without gulping, and is in part explained by the lower rate of respiration with a consequent drop in dead air space. Assuming a dead air space of 0.15 L., the effective minute ventilation would be 4.8 L. with the aid of gulping and 5.2 L.

without the aid of gulping. By gulping alone he attained the remarkable "gulping vital capacity" of 2.4 L.

CASE 4. J.D., a 30-year-old male pilot, rapidly developed paraplegia and respiratory paralysis and was hospitalized. Six weeks after the onset, he was transferred to the Respirator Center.

The initial examination showed normal pulse and blood pressure. Atrophy of all muscle groups was evident. Both upper extremities were completely flaccid, and there was no evidence of function of the intercostals, diaphragm or abdominal wall. The lower extremities were weak. He was unable to breathe unassisted for more than a few seconds and his vital capacity was not measurable on admission and had never been greater than 100 ml. During the next 10 months, the time spent in the cuirass respirator was increased as the tank respirator was gradually dispensed with. He could not be induced to use the rocking bed, however, because of nausea, weakness and sweating. Studies made to determine the reason revealed that his minute ventilation was inadequate while rocking.

In July, 1954, nearly a year after onset, the patient was taught glossopharyngeal breathing as part of the weaning program at this Center. One month later comparative ventilatory studies were made of glossopharyngeal breathing, cuirass respirator, rocking bed and unassisted breathing. These are recorded in Table 4A.

It is apparent from these studies that of the four methods of respiration only the cuirass respirator was able to supply an adequate minute ventilation. The other three methods all gave a minute volume of 5 L. or less, and it is probable that his minute ventilation requirement is somewhat above this figure.

Steady improvement in technique and stamina has been associated with an increase in minute ventilation so that breathing time has gradually lengthened (see Table 4B).

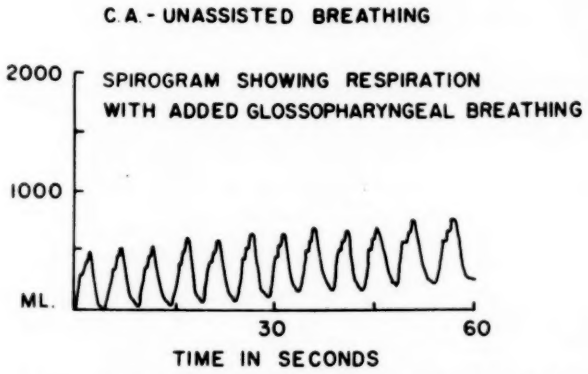

Fig. 3.—Spirogram on patient C.A. The tidal volume is 500 ml. and the respiratory rate is 12 per minute. Note that each inspiratory effort is followed by two stepladder-like increments which are the result of glossopharyngeal breathing.

TABLE 4A.—DATA ON EFFICIENCY OF UNASSISTED AND ASSISTED BREATHING IN CASE 4.
J.D., August, 23, 1954

	O_2 Uptake L./min.	*Min. Ven. L.*	*Ventilation Quotient %*	*Tidal Air L.*	*Rate Per Minute*
Huxley cuirass	0.23	6.8	3.3	0.4	17
Unassisted breathing	0.18	1.7	11.0	0.07	25
Rocking bed	0.2	5.0	4.0	0.26	19
Glossopharyngeal breathing	0.23	2.6	6.1	0.37	7

Discussion. Glossopharyngeal breathing has proved to be of aid in the rehabilitation of 4 patients with severe respiratory paralysis. With this voluntary mechanism, patients who require

artificial respiration are able to have a significantly prolonged unassisted breathing time, increase in vital capacity, tidal volume, force of cough, and increased mobility of the chest cage. This method of respiration may provide a brief rest for the fatiguing muscles of respiration; in some patients it may be the sole method of unassisted respiration. The process may be taught in from 2 days to several weeks, and patients have learned this from observing other patients on the ward, although months may be required to achieve maximum proficiency.

TABLE 4B.—DATA ON IMPROVEMENT OF EFFICIENCY OF GLOSSOPHARYNGEAL BREATHING IN CASE 4.

J.D.

	Vital Capacity with Glossopharyngeal Breathing L.	*Minute Ventilation* L.	*Unassisted Breathing Time*
8- 2-54	1.2	2.3	1 min.
8-23-54	1.3	2.6	
9-13-54	1.5	—	
9-21-54	1.7	3.8	15 min.
11- 9-54	1.9	4.8	15 min.
2- 1-55	1.5	5.0	20 min.
8-20-55	1.9	5.0	52 min.

In addition to its effects on respiration, the acquisition of this technique has produced a marked change in psychological attitude. The realization that they were again independent of respiratory aids even for a few minutes has had a great effect on morale, and has stimulated patients to make a greater effort toward their rehabilitation goals.

The fact that a tracheotomy site in one patient, thought to have healed, began to leak air during glossopharyngeal breathing calls attention to the effective intratracheal pressures which may be developed by this method. An intratracheal pressure as high as 30 cm. of water has been recorded in one patient.

The fourth patient was able to breathe for the first time without assistance since the onset of his disease as a result of glossopharyngeal respiration. His unassisted breathing time has extended from one minute in August, 1954, to 52 minutes in August, 1955. This has proven to be of great importance to him. Thus, he had lost the fear that recurred whenever chest shells were changed, attempts at unassisted breathing were made or recurrent possibility of mechanical failure came to mind. Further, he is now able to cough, call across the ward in a loud voice, receive physical therapy with manipulation of the chest, be bathed and participate in other activities without artificial respiration. This patient admits that reservations had prevented him, until recently, from producing the maximum effort toward glossopharyngeal breathing because he was unable to accept the fact, psychologically, that glossopharyngeal breathing is his sole respiratory mechanism.

Summary. Glossopharyngeal breathing (gulping, frog breathing) is a form of accessory respiration whereby the lungs may be inflated with air. The upper respiratory parts including the mouth, tongue and pharynx act as a bellows to pump air into the thorax. The soft palate and larynx and vocal cords then serve as valves to prevent escape of air during the process. Ten or 12 such gulping efforts can produce

a tidal volume adequate for resting ventilation. The method is taught to patients as part of the process of weaning from mechanical aids. Its primary value has been an increase in unassisted breathing time, vital capacity, tidal volume, force of cough and mobility of the chest cage. The glossopharyngeal technique has proved beneficial to the patients from a psychological as well as the physical aspect of the problem of rehabilitation of severe spinal poliomyelitis.

Four cases are reported. The accompanying data illustrate the sharp and rapid increase in vital capacity in these patients who learn glossopharyngeal breathing. Tables accompanying each report present sample ventilation studies.

ACKNOWLEDGMENTS: Grateful acknowledgment is made for technical assistance in the preparation of this paper to Mrs. Joan Neuhouse, Miss Antoinette Berghorn, Miss Esther Cresco. Dr. Howard Dayman, Director of the Respirator Center, made numerous helpful suggestions and provided the interpretation of the pneumotachogram. Dr. Simon Rodbard, Director of the Chronic Disease Research Institute, gave valuable advice and encouragement.

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SUMMARIO IN INTERLINGUA

Respiration Glossopharyngee Como Adjuta al Recuperation ab Poliomyelitis Paralytic

Respiration glossopharyngee es un forma de respiration accessori permittente le inflation aeree del pulmones. Le organos respiratori superior, includente bucca, lingua, e pharynge, age como un pumpa que fortia aere a in le thorace. Le palato molle e larynge e chordas vocal functiona como valvulas que preveni le escappamento del aere durante le processo. Dece o 12 tal effortios de respiration glossopharyngee pote producer un volumine de aere currente que suffice como ventilation de reposo. Le methodo es inseniate al patientes como parte del processo de dishabituation ab le adjuta mechanic. Su valor principal es su augmentation del tempore de respiration independente, del capacitate vital, del volumine de aere currente, del fortia de tusse, e del mobilitate del thorace. Le technica glossopharyngee es benefic pro le patiente tanto ben ab le puncto de vista psychologic como ab le puncto de vista physic in su effortio de rehabilitar se ab sever poliomyelitis spinal.

Es reportate quatro casos. Le datos presentate illustra le acute e rapide augmento del capacitate vital de iste patientes durante lor apprentissage del respiration glossopharyngee. Tabulas fornite pro le quatro casos presenta exemplos de studios de ventilation.

CORONARY ARTERIOSCLEROTIC HEART DISEASE IN THE YOUNGER AGE GROUP: ITS GREATER FREQUENCY IN THIS GROUP AMONG AN INCREASINGLY OLDER NECROPSY POPULATION*

By Otto Saphir, M.D.

Leonard Ohringer, M.D.

and

Herbert Silverstone, Ph.D.

(From the Department of Pathology,** Michael Reese Hospital, Chicago, Illinois)

Arteriosclerotic heart disease in the younger age group is not rare and a number of reports have appeared in the more recent literature[1,2,3]. Being responsible for the necropsy material of a large general hospital, and being particularly interested in various cardiac diseases, we noticed that over the last years there was a seemingly increased incidence in the number of cases of arteriosclerotic heart disease among our necropsy population in the younger age group. Upon questioning a number of the older physicians in the practice of Internal Medicine, they reported that they had also encountered this disease in a younger age group more often now than ever before. However, exact figures were not available.

To ascertain whether or not arteriosclerotic heart disease (AHD) in the younger age group occurs more frequently now and during the last decade than during the immediately preceding two decades, the necropsy material on patients over 20 years of age at Michael Reese Hospital over the last 34 years (1920 to 1939, 1940 to 1949 and 1950 to 1953) was restudied. By arteriosclerotic heart disease (AHD), as used in this study, is meant coronary arteriosclerosis or atheromatosis with or without myocardial fibrosis or infarction. No differentiation was made in regard to the severity of lesions, and also no attention was paid as to whether or not the patients had or had not had pertinent clinical findings. However, cases which had been labeled "minimal coronary arteriosclerosis" were not included in this study. This report concerns only necropsies performed on patients who were 20 years of age or older.

The total number of necropsies on adults during 1920 to 1939 was 2,696. Eight hundred and thirty-six of these patients (31%) had arteriosclerotic heart disease. During 1940 to 1949 there were 2,764 necropsies. Eight hundred and seventy-eight (31.8%) of these showed AHD. It is interesting that the percentage of AHD among our necropsy population remained just about the same over this 30-year period. During the period 1950 to 1953 there were

*This study was supported in part by the U. S. Public Health Service Grant-in-Aid H–1507 and in part by the Byron C. Sharpe Research Fund.

**This Department is supported in part by the Michael Reese Research Foundation.

This paper was read before the American Association of Pathologists and Bacteriologists at their Fifty-second Annual Meeting in Houston, Texas, April, 1955.

1,572 necropsies, 451 (28.7%) of which disclosed AHD. The lower percentage during this period may be explained on the fewer number of necropsies which were performed during this shorter interval. The preponderance of males among our necropsy population was striking. Out of the total of 2,165 patients with AHD there were 1,403 males and 762 females. Figs. 1 and 2 are included to show these figures graphically.

In the following, the incidence of AHD in the necropsied individuals in the age group from 20 to 49 will be given as found during these three periods. This will be compared with the over-all age distribution of the necropsy population during the time intervals under discussion. Possible etiologic factors will also be mentioned.

As just stated, AHD over the period 1920 to 1939 was encountered 836 times, while the total necropsy popula-

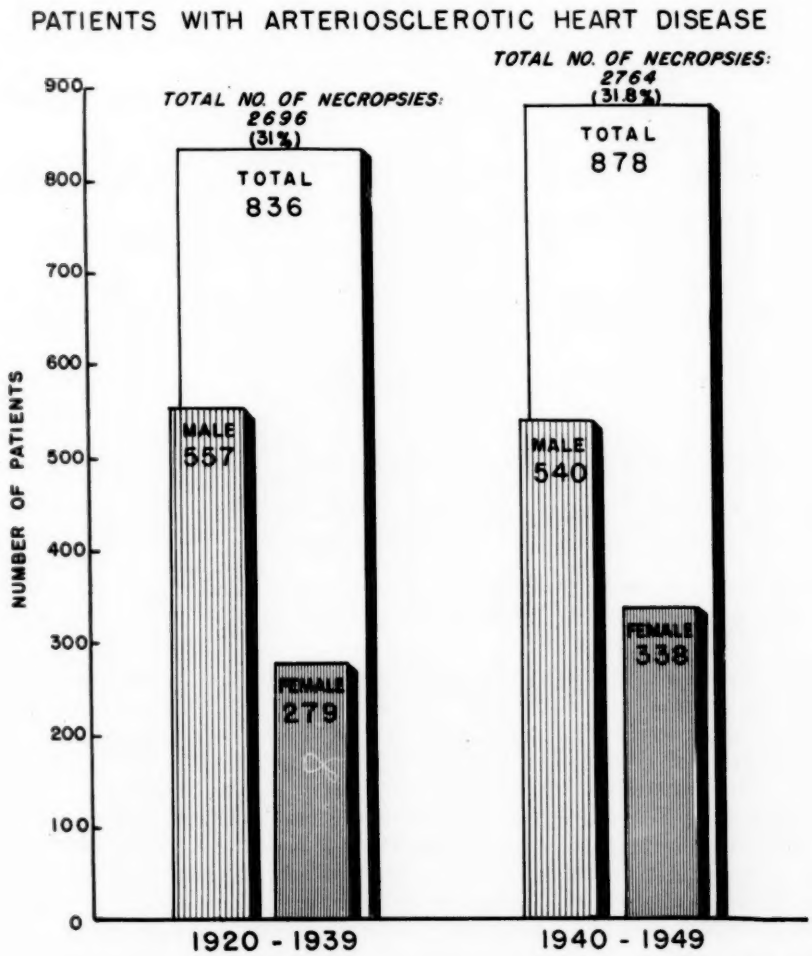

Fig. 1.—Number, relative frequency, and sex distribution of all necropsied adults with arteriosclerotic heart disease during 1920–1939 and 1940–1949.

tion during the same time interval was 2,696. Of these 836 cases with AHD there were 61 patients under 50 years of age. In contrast, during the 1940 to 1949 period, when there were 878 cases with AHD among a necropsy population of 2,764, 107 patients were under 50 years of age. The total number of necropsies performed during 1950 to 1953 was 1,572, of which 451 (28.7%) were cases with AHD. Fifty-two (11.5% of the latter) were under 50 years of age.

Table 1 is included to show the more detailed age distribution of AHD as occurring in the three decades from 20 to 49 during the consecutive intervals 1920 to 1939, 1940 to 1949, and

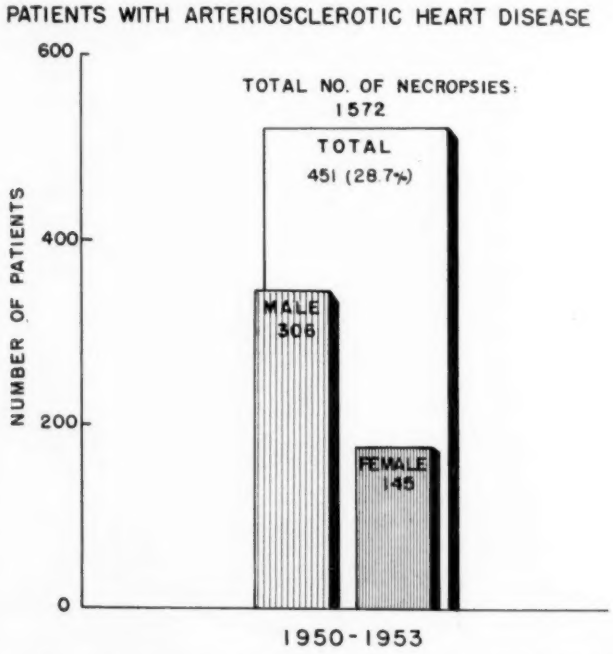

Fig. 2.—Number, relative frequency, and sex distribution of all necropsied adults with arteriosclerotic heart disease for the period 1950 through 1953.

the two decades 1920 to 1939 and during the immediately following 10 years were remarkably close, 2,696 and 2,764, and it is interesting that the percentage of cases with AHD was also about the same, 31% and 31.8%. However, there was a significant difference in the number of patients with AHD under 50 years amounting to 61, or 7.3% of all AHD patients during 1920 to 1939, and to 107 or 12.2% of patients with AHD from 1940 to 1949. During 1950 to 1953 the total number of necropsies was 1,572, of which 451 (28.7%) were cases with AHD. Fifty-two (11.5% of the latter) were under 50 years of age. It shows in particular the increase in the incidence of AHD in the 40 to 49 year age group, during 1940 to 1949.

Although there seems to be no corresponding increase during 1950 to 1953, it must be remembered that this interval covers only a 4-year period. Projected over a 10-year period there would also be a considerable increase. Table 2 shows the increase in AHD expressed on a percentage basis.

The increase in all age classes under

50 years is obvious. As is also shown, there is a decrease in the relative incidence of AHD in patients 50 years and over. The AHD frequency relative to only necropsied individuals over 50 has declined from 46.6% to 29.1% (Table 2, last row). It seems clear that during the period subsequent to 1940 a higher proportion of the AHD cases occurred in the under 50 age group. Furthermore, the frequency of AHD patients under 50 relative to all necropsies also increased (2.27% during 1920 to 1939, and 3.87% from 1940 to 1949) (Table 3).

Table 4 is included to show the relative frequency of AHD in necropsies on adults under 50 years of age expressed in percentage to all cases with AHD. The jump from 7.3% to 12.2% and to 11.5% during only a 4-year period seems significant.

The increase in AHD in the younger age group and its relative decrease in patients over 50 would not be particularly significant if at the same time also more necropsies had been performed on a younger age group. However, just the opposite is true. The age distribution of all adult necropsies for the years 1920 to 1939, 1940 to 1949, and 1950 to 1953, is given in Table 5.

TABLE 1.—AGE DISTRIBUTION OF ARTERIOSCLEROTIC HEART DISEASE (AHD) DURING THE CONSECUTIVE INTERVALS 1920 to 1939, 1940 to 1949, 1950 to 1953

	Numbers of Necropsied Individuals with AHD		
Age	*1920 to 1939*	*1940 to 1949*	*1950 to 1953*
20 to 29	6	7	5
30 to 39	15	25	9
40 to 49	40	75	38
20 to 49	61	107	52
50 and over	775	771	399
Total	836	878	451

TABLE 2.—AGE DISTRIBUTION OF ARTERIOSCLEROTIC HEART DISEASE (AHD) DURING THE CONSECUTIVE INTERVALS 1920 to 1939, 1940 to 1949, 1950 to 1953

	% of Necropsied Individuals in the Age Class		
Age	*1920 to 1939*	*1940 to 1949*	*1950 to 1953*
20 to 29	2.6	4.9	10.6
30 to 39	4.6	11.5	13.8
40 to 49	8.3	18.8	41.7
20 to 49	5.9	14.1	25.5
50 and over	46.6	38.4	29.1

TABLE 3.—AGE DISTRIBUTION OF ARTERIOSCLEROTIC HEART DISEASE (AHD) DURING THE CONSECUTIVE INTERVALS 1920 to 1939, 1940 to 1949, 1950 to 1953

	% of All Necropsied Adults		
Age	*1920 to 1939*	*1940 to 1949*	*1950 to 1953*
20 to 29	0.23	0.25	0.32
30 to 39	0.56	0.90	0.57
40 to 49	1.48	2.71	2.42
20 to 49	2.27	3.87	3.31
50 and over	28.7	27.9	25.4
Total (All ages)	31.0	31.8	28.7

TABLE 4.—RELATIVE FREQUENCY OF AHD IN NECROPSIED ADULTS UNDER 50 YEARS OF AGE, AS PERCENTAGE OF ALL CASES WITH AHD

	% of All Necropsied Adults		
Age	*1920 to 1939*	*1940 to 1949*	*1950 to 1953*
20 to 29	0.7%	0.8%	1.1%
30 to 39	1.8	2.8	2.0
40 to 49	4.8	8.6	8.4
20 to 49	7.3%	12.2%	11.5%

TABLE 5.—AGE DISTRIBUTION OF ALL NECROPSIES OF ADULTS DURING THE CONSECUTIVE INTERVALS 1920 to 1939, 1940 to 1949 and 1950 to 1953

	Necropsies during the Years					
	1920 to 1939		*1940 to 1949*		*1950 to 1953*	
Age	*Number*	*%*	*Number*	*%*	*Number*	*%*
20 to 29	227	8.4	142	5.1	47	3.0
30 to 39	327	12.1	218	7.9	65	4.1
40 to 49	481	17.8	399	14.4	91	5.8
20 to 49	1035	38.3	759	27.5	203	12.9
50 and over	1661	61.7	2005	72.5	1369	87.1
Total	2696	100.0	2764	100.0	1572	100.0

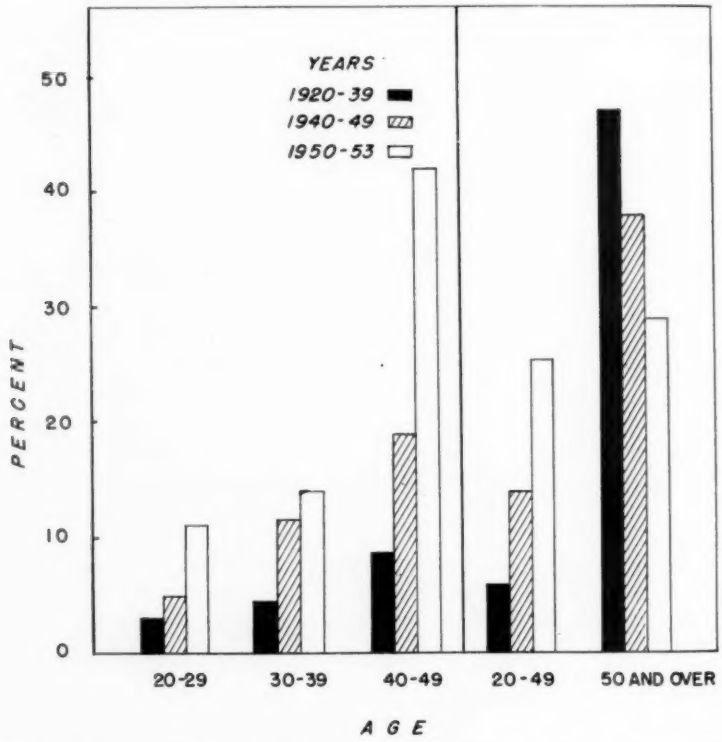

Fig. 3.—Relative frequency of arteriosclerotic heart disease in each age class per 100 necropsies in that age class. Illustrating the increase in the age classes under 50, and the decrease in the over-50 class.

As can be seen, between 1920 and 1939, 38.3% of all necropsies were performed on individuals between 20 and 49 years old; while from 1940 to 1949, 27.5% and during 1950 to 1953 only 12.9% were under 50. Each of the three age decades, 20 to 29, 30 to 39, and 40 to 49, show about the same relative decrease.* There was a corresponding increase in the ages of our necropsy population in the older age group over the last 34 years. It is obvious that relative to the base years 1920 to 1939, the necropsy population has changed so that a decreased proportion of all those necropsied were less than 50 years old. This makes the increase in AHD in the younger age group more significant.

In comparing the percentage of AHD in necropsied individuals in the respective age class (Table 2) it immediately becomes evident that, employing 1920 to 1939 as a base, there has been an increase in the frequency of AHD among necropsied individuals in the age groups under 50: from 5.9% in the years 1920 to 1939, to 14.1% during 1940 to 1949, to 25.5% in the years most recently evaluated (Table 2). These changes are statistically significant.** Of all the adult necropsies during the base period, 1920 to 1939, 2.27% were under 50 and had AHD; the corresponding data for 1940 to 1949 and 1950 to 1953 were 3.87% and 3.31%, respectively, a small but statistically significant increase** (Table 3).

The frequency of all AHD necropsies relative to *all adult necropsies* was about the same in 1940 to 1949 as in 1920 to 1939 (about 31%) and the same is true for the frequency of AHD necropsies among those *over 50 years* of age relative to *all adult necropsies* (about 28%) (Table 3). The years 1950 to 1953, however, reveal a small decrease in the relative frequency of AHD among the total necropsies for all adults and also for adults over 50. This may be due to the short interval covered and perhaps also in part to the recent introduction of procedures which prolong slightly the lives of those suffering AHD.

Figure 3 shows graphically the relative frequency of AHD in each age class per 100 necropsies in that age class. It further illustrates the increase in the age classes under 50 over the three time periods and the decrease in the over 50 class.

From the above it is clear that in the over 50 age group the AHD frequency relative to *all adult* necropsies in general has changed little but that the AHD frequency relative to *only necropsied individuals over 50* has declined sharply from 46.6% to 29.1% (Table 2, last row). This is principally consequent to the shift in total necropsies into the over 50 year age group. Thus, the over-all picture is of a shift in the total necropsy population toward older individuals and a small but

*The decrease in relative frequency is of statistically significant magnitude (Chi square test, P less than 1%).

This and following references to statistical significance were based on limits of the expectations from Binominal and Poisson distributions (Statistical Tables for Biological Agricultural and Medical Research, **Fisher, R. A., and **Yates, F.,** London: Oliver and Boyd, Ltd., 1943, 2nd Ed. Table $VIII_1$). The years 1920 to 1939 were presumed to be a stable base; the probability that relative frequencies observed during 1940 to 1949 and 1950 to 1953 could have derived from populations in which the actual relative frequency was the same as that of the 1920 to 1939 period was evaluated. A probability less than 2.5% was taken to denote statistical significance. Rigidly the test may not be appropriate since there are other major obvious differences in the necropsy populations. Nevertheless, it is believed that the inferences made are in the main correct.

distinct trend in the opposite direction for AHD.

From the above it is thus clear that the total AHD frequency has not changed, while there is an increase in its occurrence in the younger age group, the most striking increase in frequency occurring in the 40 to 49 age group. This occurred at a time when the necropsy population became increasingly older. Is it possible that patients with AHD die earlier now than before? A spot check does not disclose a significant difference between the severity of the lesions in the various periods of time. The shift in the ages of the necropsy population may perhaps be linked to the military draft of men in the younger age group, those drafted or having been in service being taken care of in military hospitals, leaving more room in private institutions for the care of the older age group. Perhaps also the use of the antibiotics may be in part at least responsible for the increasing life span and therefore for the shift towards the older age group.

In the light of recent investigations as to the cause of one type of AHD, atheromatosis of the coronary artery, an attempt was made to see whether or not intake of foods rich in cholesterol and other lipids might perhaps somehow be linked to the increase in AHD in the younger age group. However, because of the variegated group of patients seen in a general hospital, and because the clinical records do not contribute any data in this respect, no statement in regards to food intake and increased frequency of AHD in the younger age group can be made at present. Yet it may be significant that there has been a rise in the per capita consumption of eggs, and some lipid-containing dairy products over the years. Table 6 with figures taken from the Agriculture Handbook #62, U. S. Department of Agriculture, is included to show the rise of per capita consumption of these foods.

It is noteworthy that while the general population used more of these foods over the 32 years, the incidence of AHD among the *total* necropsy population has not changed appreciably. There should be other causes besides diet which may be responsible for the increase in AHD among the younger age group. An investigation of these is in progress.

TABLE 6.—PER CAPITA CONSUMPTION OF EGGS, AND SOME LIPID-CONTAINING DAIRY PRODUCTS FOR THE YEARS 1930 TO 1952*

Years	*Eggs*	*Milk Fat in Pounds*	*Cheese in Pounds*	*Ice Cream in Pounds*
1930	327	38.4	4.6	9.6
1935	276	38.6	5.2	8
1940	314	40.8	5.9	11.2
1945	397	49.1	6.6	15.4
1950	383	46.4	7.6	17
1952	407	47.3	7.7	17.5

* Taken from Agriculture Handbook No. 62, U.S. Dept. of Agriculture.

Summary. An investigation of the incidence of arteriosclerotic heart disease in the younger age group of a large necropsy population over the last 34 years discloses that the total arteriosclerotic heart disease frequency has not changed. However, there is an increase in its occurrence in the younger age group, the most striking increase in frequency occurring between the ages of 40 to 50. During the same period of time the necropsy population has become increasingly older. Since

arteriosclerotic heart disease among the total necropsy population has not changed appreciably, factors other than diet may be responsible for this increase in arteriosclerotic heart disease among the younger age group.

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SUMMARIO IN INTERLINGUA

Morbo Cardiac a Sclerosis de Arteria Coronari in le Gruppo de Etate Minus Avantiate: le Plus Alte Frequentia del Morbo in Iste Gruppo Inter un Population Necroptic de Etates Progressivemente Avantiante

Un investigation del frequentia de arteriosclerotic morbo cardiac in le gruppo de etate minus avantiate inter un extense population necroptic, observate durante le passate 34 annos, revela que le frequentia total de arteriosclerotic morbo cardiac ha remanite incambiate. Tamen, il ha un augmento del morbo in le gruppo de etate minus avantiate, con le plus frappante augmento concentrate inter le etates de 40 e 50. In le periodo sub consideration, le etate del population necroptic avantiava progressivemente. Proque le frequentia de arteriosclerotic morbo cardiac in le population necroptic total non monstra ulle alteration significative, factores altere que le dieta es possibilemente responsabile pro le augmento de arteriosclerotic morbo cardiac in le gruppo de etate minus avantiate.

ELECTROCARDIOGRAPHIC OBSERVATIONS IN PATIENTS WITH CEREBROVASCULAR ACCIDENTS*

REPORT OF 12 CASES

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Electrocardiographic changes have been observed by a number of authors in patients with cerebrovascular accidents[5-8]; recently, however, Burch and co-workers[4] have reported an interesting series of cases with "distinctive electrocardiographic patterns." These consisted of rather marked QT prolongation and prominent T and U wave alterations. The purpose of this paper is to report our findings in a series of 12 patients with various cerebrovascular accidents.

Material and Methods. During the period between October 1, 1954, and February 1, 1955, electrocardiograms were taken routinely on all patients with cerebrovascular accidents admitted to the Graduate Hospital of the University of Pennsylvania. Twelve patients were observed with electrocardiographic abnormalities localized in the T wave and T–U segments. These were studied in the following manner: 1) A detailed cardiovascular history was obtained either from the patient or from the patient's family. 2) The patient was studied for clinical evidence of heart disease antedating the present illness. 3) Corroborative clinical and laboratory data were obtained to confirm the cerebrovascular diagnoses. 4) Serum electrolytes including sodium, chlorides, and potassium were drawn simultaneously with the initial electrocardiogram and at frequent intervals thereafter, in 10 of the 12 patients. Blood pH was determined on two of these patients. 5) The blood pressures were recorded twice daily during the period of observation and rectal temperatures were recorded every 4 hours. 6) In addition, careful investigation was made regarding the presence of, or the frequency of, vomiting, administration of drugs taken which might affect the electrocardiogram, and the food intake of the patient for 48 to 72 hours preceding hospitalization.

All electrocardiograms were taken within 24 hours following admission to the hospital. When possible, these tracings were observed at varying intervals for a period of 2 to 3 weeks.

Serum sodium and potassium were determined by the flame photometric method using Lithium as the internal standard on the Perkin-Elmer flame photometer. Serum chlorides were determined by the electrometric titration method of Seligson[10]. Blood pH was determined using a glass electrode under anaerobic conditions on the Beckman pH meter; the temperature was corrected to 38°

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C. The range of normal laboratory values in this hospital is as follows: serum sodium 130 to 147 mEq. per liter; serum chloride 90 to 107 mEq. per liter; serum potassium 3.5 to 5.2 mEq. per liter.

Results. The ages of the 12 patients studied ranged from 41 to 70 years, with an average age of 56.4 years. There were 7 males and 5 females. Of the 12 patients, 11 were found to have clinical evidence of heart disease prior to admission to the hospital. There were 2 patients with hypertensive cardiovascular disease, 7 with arteriosclerotic cardiovascular disease and 2 patients who manifested both hypertensive and arteriosclerotic cardiovascular disease. Two of these 11 patients (Cases 5 and 8) presented historical evidence of a healed myocardial infarction.

TABLE 1.

No.	*Case*	*Age*	*Diagnosis*	*Significant Findings (other than history and physical exam.)*	*Period from Onset of Cerebrovascular Accident to Initial EKG*
1.	L.B.	43	Intracerebral and Subarachnoid Hemorrhage	Bloody Spinal Fluid	Same day
2.	M.C.	54	Subarachnoid Hemorrhage	Bloody Spinal Fluid	Same day
3.	M.H.	62	Subarachnoid Hemorrhage	Bloody Spinal Fluid	Same day
4.	F.D.	50	Subarachnoid Hemorrhage	Bloody Spinal Fluid	Same day
5.	E.D.	56	Cerebral Thrombosis	Focal EEG Abnormalities	5 days
6.	G.C.	69	Cerebral Edema	Increased Spinal Fluid Pressure	5 days
7.	F.C.	63	Subarachnoid Hemorrhage*	Bloody Spinal Fluid	Same day
8.	G.D.	51	Subarachnoid Hemorrhage	Bloody Spinal Fluid	5 days
9.	S.M.	70	Subarachnoid Hemorrhage	Bloody Spinal Fluid	6 days
10.	M.W.	41	Subdural Hematoma*	None	5 days
11.	S.Y.	63	Intracerebral and Subarachnoid Hemorrhage, Subdural Hematoma*	Bloody Spinal Fluid	Same day
12.	R.Z.	55	Subarachnoid Hemorrhage	Bloody Spinal Fluid	Same day

* Traumatic in origin

TEMPORAL RELATIONSHIP BETWEEN THE CEREBROVASCULAR ACCIDENT AND THE ELECTROCARDIOGRAPHIC ABNORMALITIES. Because of the variability of the time interval intervening between onset of the illness necessitating admission to the hospital, the electrocardiogram and the electrolyte studies were obtained within varying periods of time following the actual onset of the cerebrovascular accident. In 7 of the 12 patients, the electrocardiographic abnormalities were first observed within 24 hours following the onset of the acute cerebrovascular accident. In the remaining 5 patients, the electrocardiographic alterations were detected within one week following onset of the cerebrovascular accident; this delay usually resulted from delayed admission to the hospital. In 3 patients serial electrocardiograms were taken over a period of 2 to 3 weeks in an attempt to determine the duration of the observed changes. The various types of cases studied are shown in Table 1.

FOOD INTAKE PRIOR TO HOSPITALIZATION. The food intake of 6 of the 12 patients was reported as good prior to the acute cerebrovascular accident. Five additional patients apparently had an adequate food intake; each gave a history of vomiting at least once before admission. The remaining patient (Case 10) presented a history of repeated episodes of vomiting and was also found to have had an inadequate food intake for the 48 hours preceding hospitalization.

DRUGS PRIOR TO ADMISSION. Two of the 12 patients studied had been on main-

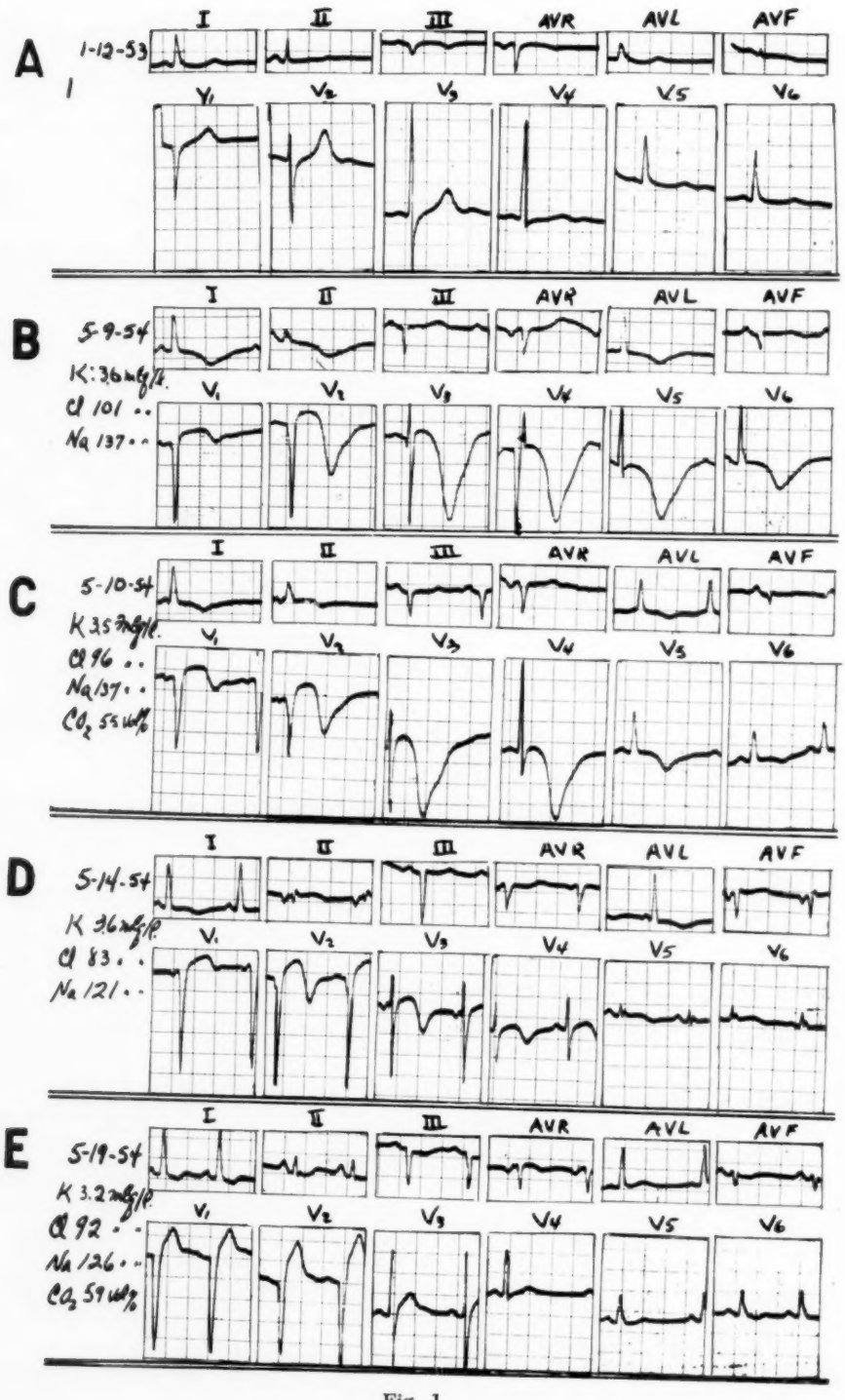

Fig. 1.

(Legend on opposite page)

tenance doses of digitalis prior to hospitalization. Continuation of this medication failed to influence the electrocardiographic alterations.

CHANGES IN BODY TEMPERATURE. It is a common experience to observe hyperpyrexia, particularly terminally, in association with cerebrovascular accidents. However, our patients were studied fairly early in their illness and the electrocardiograms on all patients were taken when the body temperatures were essentially normal.

ELECTROCARDIOGRAPHIC ABNORMALITIES. The electrocardiographic changes observed in our 12 cases consisted of marked prolongation of the ST interval (ventricular repolarization) and alterations in the amplitude and direction of the T waves. Deep and wide inversions of the T waves, which probably contained an inverted U wave were observed in 11 patients (Figs. 1 and 3). In one patient where the T waves were upright a prolonged QT and a prominent upright U wave were observed. The prolongation of the ST intervals (ventricular repolarization) above the normal values[1] resulted from a widening of the T waves and, in some cases, merging of the T wave with a prominent U wave. The T wave inversions were most often seen in standard Leads I and II and in the left precordial leads (V_{4-6}), but at times were observed in other leads (aV_L, aV_F, and V_{1-3}). Table 2 summarizes the abnormalities observed in the 12 patients.

Case 3 (M.H.) developed a myocardial infarction toward the end of her period of observation, which was confirmed by a postmortem examination. The electrocardiogram showed a QS configuration with RS–T segment deviations and T wave changes suggesting an acute anteroseptal myocardial infarction. The T–U pattern manifested by this patient was more characteristic of that observed with a subarachnoid hemorrhage in B and C of Fig. 1, while the pattern in D and E was more characteristic of a myocardial infarction. The latter cannot, however, be entirely excluded as the sole cause for these electrocardiographic alterations

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Fig. 1.—M.H., a 62-year-old white female with a long history of hypertensive cardiovascular disease was hospitalized on May 9, 1954, because of an acute spontaneous subarachnoid hemorrhage. Within several hours following admission she complained of severe substernal compression. The tracing taken on January 12, 1953, shows changes indicating left ventricular hypertrophy and digitalis effect and serves as the control.

On May 9, 1954, there is a QS configuration in V_1 and V_2 with RS–T segment elevation in V_{1-3} and depression of this segment in aV_L, V_5 and $_6$. Note the deep T wave inversion in leads I, II, aV_L and V_{1-6}. Note the marked widening of the T waves, and in the ascending limb of the T wave in V_{2-5}, there is a slight irregularity on the ascending limb of the T wave, suggesting that a U wave makes up a terminal portion of the T wave. The QT interval was 0.72 second and the heart rate 75 per minute. The serum electrolytes are within the normal range. The configuration of the inverted T waves from V_{2-6} in B and C resemble the pattern that has been observed resulting from subarachnoid hemorrhage. In D and E the pattern changes somewhat to that more characteristic of myocardial infarction. The difference between C and D is rather striking. In the latter, the inverted T waves are no longer deep and the QT segments are of relatively normal length. The chief evidences of R–T deviation are observed in $V_{2 \text{ and } 3}$ of D and $V_{1 \text{ and } 2}$ of E. At necropsy a small infarction (1½ cm.) was observed localized to the anteroseptal portion of the left ventricle close to the interventricular septum. The infarction was acute and relatively recent.

In summary, it is felt that the changes observed on May 9 and May 10 were predominantly those of subarachnoid hemorrhage, while those of May 14 and May 19 were more characteristic of a myocardial infarction.

TABLE 2.—CORRELATION OF ELECTROCARDIOGRAPHIC FINDINGS AND ELECTROLYTES

		Electrocardiographic Findings			*Electrolytes (serum)*				
No.	*Case*	*QT Duration*	*T Waves*	*Other Changes*	*Na mEq./L.*	*K mEq./L.*	*Cl mEq./L.*	*CO_2 Vol.%*	*BUN mg./100 ml.*
1.	L.B.	Moderately prolonged	Inverted in I, II, aVL, V_{2-6}	None	136	3.7	95		9
2.	M.C.	Moderately prolonged	Inverted in I, II, III, aVF, V_{4-6}	None	141	3.8	100		12
3.	M.H.	Markedly prolonged	Inverted in I, II, V_{1-6}	Acute anteroseptal infarction, left ventric. hypertrophy	137	3.6	96	50	11
4.	F.D.	Moderately prolonged	Tall and wide in I, II, V_{2-6} (all upright)	None	117	4.2	78		11
5.	E.D.	Moderately prolonged	Inverted in I, II, aVF, U_{5-6}	Old anterior myocardial infarction, left ventric. hypertrophy	139	4.9	100	57	15
6.	G.C.	Slightly prolonged	Inverted V_{1-4}	None	—	—	—	—	30
7.	F.C.	Slightly prolonged	Inverted in I, II, III, aVF, V_{4-6}	Left ventric. hypertrophy	—	—	—	—	—
8.	G.D.	Moderately prolonged	Inverted in II, III, aVL, V_{5-6} and low amplitude in I	Left ventric. hypertrophy	127	4.0	90	48	11
9.	S.M.	Moderately prolonged	Inverted in II, III, aVF, V_{1-3}	Right axis deviation	153	4.1	110	47	18
10.	M.W.	Slightly prolonged	Inverted in I, aVL, V_{2-6}	None	134	3.0	90		
11.	S.Y.	Moderately prolonged	Inverted in V_{1-4}	None	143	3.7	110	50	15
12.	R.Z.	Moderately prolonged	Inverted in I, II, III, aVL, aVF, V_{1-6}	None	139	4.9	103	42	19

(Fig. 1). Eight of our 12 patients died; postmortem examinations were performed on three of these.

In 3 patients where the periods of observation were sufficiently prolonged, serial electrocardiograms showed a gradual return of the changes to a more normal configuration as the clinical state of the patient improved; usually this occurred over a period of 2 to 3 weeks.

SERUM ELECTROLYTES. Serum electrolytes, obtained simultaneously with the first electrocardiogram in 10 of the 12 cases, are recorded in Table 2. Blood pH was determined on 2 of these 10 cases. All studies coincided with the initial electrocardiographic abnormalities in each patient. Three of the 10 patients showed evidence of electrolyte imbalance. Case 10 (M.W.) had a mild hypopotassemia on admission to the

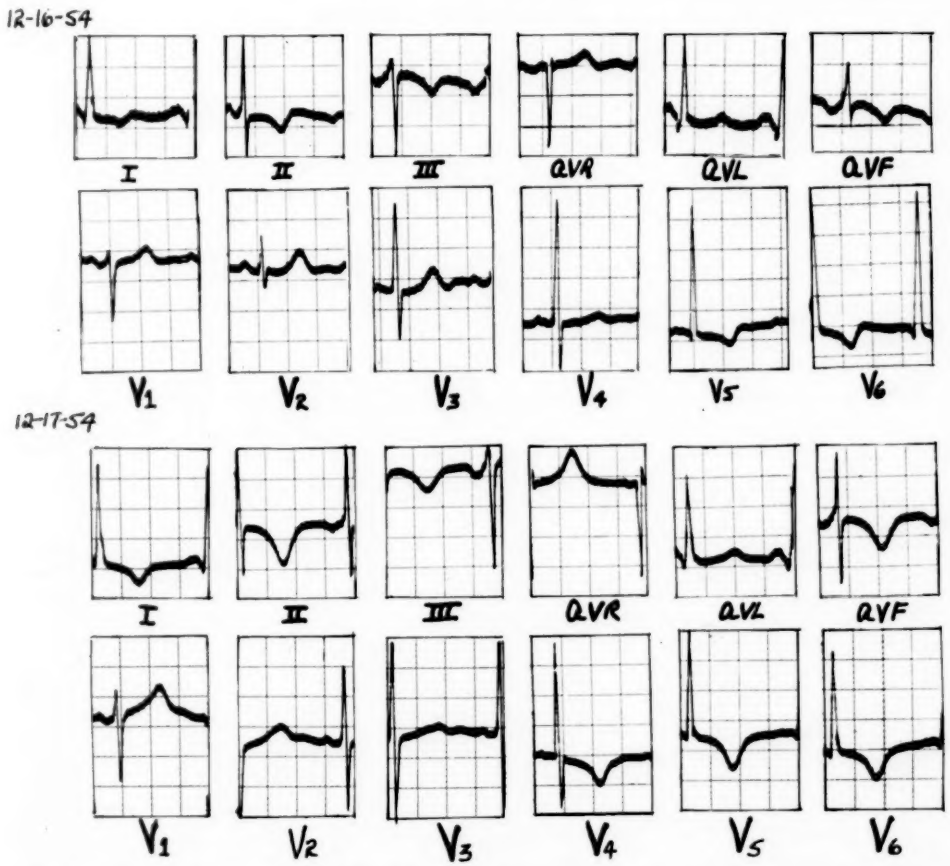

Fig. 2.—F.C., a 63-year-old white female with a long-standing history of hypertensive cardiovascular disease suffered a spontaneous subarachnoid hemorrhage approximately 9 hours prior to the initial electrocardiogram on December 16, 1954. There is evidence of left ventricular hypertrophy, the heart rate is 100 per minute, and the QT interval measures 0.34 second. Note the T wave inversion in leads I, II, III, aV_F, V_5 and $_6$. On the following day the heart rate was 83 per minute; the QT interval has increased to 0.4 second and there is more pronounced T wave inversion in leads I, II, III, aV_F and V_4 and $_6$. Note also the prominent upright U wave in V_1 and $_2$.

hospital; this was the only patient to give a history of repeated bouts of vomiting and poor food intake for the several days prior to entering the hospital. Of the two other cases, one (Case 4, F.D.) showed a moderate hyponatremia and one (Case 9, S.M.) manifested a mild hypernatremia and hyperchloremia, probably as a result of dehydration. The blood pH in Cases 4 and 9 was within the normal range. Case 3 (M.H.), with striking electrocardiographic changes, who presented both a subarachnoid hemorrhage and a myocardial infarction, clinically, failed to show evidence of significant changes in the serum electrolyte values during the period.

Discussion. The most frequently observed electrocardiographic abnormalities were marked prolongation of the ST interval (ventricular repolarization) and deep, wide T wave (T–U wave) inversions (Figs. 1 to 3). Although much less frequently encountered (1 case) a prolonged QT interval with a wide and tall upright T wave and a prominent U wave was also seen. The duration of electrical systole in several cases occupied the entire interval up to initiation of the next succeeding atrial impulse. In our patients the changes were most commonly observed in association with subarchnoid and intracerebral hemorrhages; this confirms the previously reported findings[4].

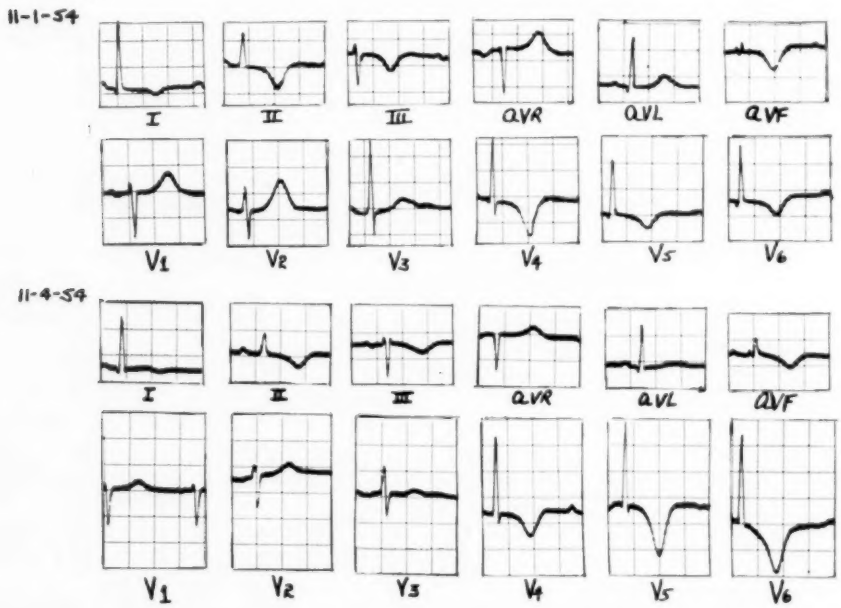

Fig. 3.—M.C., a 54-year-old white female was hospitalized on November 1, 1954, because of a spontaneous subarachnoid hemorrhage, occurring some 10 to 12 hours prior to the electrocardiogram. Note the T wave inversions in leads I, II, III, aV_F and V_4 and $_6$. The heart rate was 80 per minute and the QT duration 0.42 second. Three days later on November 4, 1954, the T wave inversion is less deep in the standard limb leads and more pronounced in the left precordial leads (V_{4-6}). The heart rate is 84 per minute and the QT duration 0.44 second. An upright U wave is present in V_2 whereas the wide deeply inverted T waves probably also contain a U wave.

While electrolyte imbalance, particularly *hypopotassemia*, can produce electrocardiographic changes similar to those observed[3,9], *hypopotassemia* was ruled out in 9 of the 10 patients by the presence of a normal serum potassium. In the remaining patient, (Case 10), the laboratory determination confirmed the presence of hypopotassemia, which was anticipated from the history of repeated bouts of vomiting and a poor dietary intake. However, the electrocardiographic abnormalities became more marked as the clinical condition of the patient deteriorated, although the serum potassium deficit had been corrected with intravenous potassium chloride. In 10 of our 12 patients, there was no apparent correlation between the electrocardiographic findings and the serum electrolytes (namely, sodium, chlorides, and potassium).*

Neither hypothermia nor hyperpyrexia was present during the period when the electrocardiographic abnormalities were observed. The blood pressure records of these patients failed to show significant changes during the period when the electrocardiographic abnormalities were observed. None of the patients appeared clinically to be in a state of shock prior to the recording of the electrocardiographic alterations.

Of the 3 patients on whom postmortem examinations were performed, one showed evidence of an acute myocardial infarction (Case 3, M.H.). Fortunately, this patient was conscious and presented a rather typical picture of acute myocardial infarction. There was no evidence of myocardial infarction in the other 2 cases necropsied. In a number of the remaining patients, a subendocardial (nontransmural) type of myocardial infarction could not be entirely excluded as a possible primary, or contributory, factor toward the development of the type of electrocardiographic abnormalities found. The clinical picture of acute myocardial infarction would, of course, be generally obscured or greatly modified by the stuporous to comatose state of the patient with an acute cerebrovascular accident (that is, subarachnoid hemorrhage). We do not, however, have any reason to believe that a myocardial infarction occurred during the period of observation in any of our patients, except in the single case mentioned above on whom necropsy confirmed the clinical impression.

CAUSES OF ELECTROCARDIOGRAPHIC CHANGES. The causes of the electrocardiographic changes observed are not altogether clear. The causes of prolongation of the ST interval and T wave changes (ventricular repolarization) are manifold[2] and are frequently difficult to determine. Some of the possible causes of the alteration in this group follow: a) Hypopotassemia appears unlikely to be the causative factor in these cases as indicated by the serum electrolyte determinations. b) The presence of myocardial infarction or an ischemic process may be responsible for these changes in some few cases; however, in most of these there was nothing to suggest such a process. Moreover, the presence of anoxia which is a frequent cause of such changes was not present in the majority of the cases studied. c) Cerebrovascular accidents are accompanied by profound disturbances which involve directly or indirectly various portions of the brain. These may indirectly affect cardiac function. The inhibitory and augmentary centers lie in close proximity to

*Although there was no correlation between the prolonged ST segments and the serum electrolyte values, this does not entirely rule out the possibility of alterations of electrolytes in the heart itself which are not always mirrored by the serum electrolyte picture.

each other in the medulla oblongata in the floor of the fourth ventricle. These centers are affected by impulses which arise from various parts of the body and include the following: intrinsic reflexes which arise from various portions of the cardiovascular system and extrinsic reflexes which originate in the extravascular receptors. In addition, the cardioregulatory centers are also influenced by impulses arising from the hypothalamus and cortex. Furthermore, the hypothalamus may affect the cardiac mechanism through its influence on the endocrine system, particularly on the thyroid and adrenal glands. Derangement of electrolyte and fluid balance may result directly or indirectly from the cerebral damage and indirectly affect the heart. Alteration in cerebral function by the various mechanisms mentioned may indirectly produce functional alterations in the heart muscle which would result in electrocardiographic changes.

Their presence, however, is another indication of the close connection between the brain and the cardiovascular system through neural, humoral, electrolyte and endocrine systems.

Summary. Although electrocardiographic abnormalities associated with cerebrovascular accidents had been observed in the past, these changes were not described in detail until relatively recently. The 12 patients reported with various cerebrovascular accidents, principally subarachnoid hemorrhage, showed prolongation of the QT interval and abnormally wide and frequently inverted T waves (T–U waves). There was no apparent correlation between the electrocardiographic abnormalities and the serum electrolytes, the body temperature or the blood pressure in our cases. The exact causes of these electrocardiographic findings are not definitely known at the present time; the various factors which may be operative in producing these changes are discussed.

ACKNOWLEDGMENTS: We wish to thank the late Dr. Joseph C. Yaskin, the resident House Staff Officers on the Neurology Service and Dr. David Seligson for their cooperation in this study. We are grateful for the help of Miss Margery Shoemaker, Assistant to the Record Librarian, Miss Gertrude Hanauer, at the Graduate Hospital of the University of Pennsylvania.

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(Interlingua on page 518)

THE MECHANISM OF COPPER DEPOSITION IN THE LIVER IN HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE)

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In recent years numerous studies on the metabolic abnormalities in hepatolenticular degeneration (HLD) have focused attention on the aminoaciduria, cupruria, peptiduria, and abnormalities in copper metabolism in this disease. The data collected to date have been interpreted, however, in markedly divergent ways so that attempts at formulation of a pathogenesis for this disease have met with little success[1-4,11,13]. The concepts that govern thinking concerning the pathogenesis of HLD are embodied in two hypotheses. The first holds that HLD is the result of a congenital familial defect due to over-absorption of copper from the gastrointestinal tract leading to toxic cirrhosis, renal tubular damage, and central nervous system poisoning. The deposition of copper in the liver and other organs in spite of a normal, or even lowered, plasma total copper level is ascribed to the fact that the bulk of plasma copper in patients with HLD is "direct-reacting," or nonceruloplasmin copper. Hence according to this concept deposition of copper in tissues occurs because of the different physical chemical state of plasma copper in this disease[1-3,11].

The second hypothesis (advanced by one of us)[13] focuses attention on the chronic aminoaciduria, the specific peptiduria[14] and the peptide copper chelate that represents the form in which copper is excreted in the urine. This hypothesis envisages HLD as a genetically determined, generalized defect of protein metabolism in which abnormal tissue proteolytic activity leads to the formation of protein or polypeptide residues with high affinity for copper binding. Incomplete metabolism of these proteins in tissues leads to the excretion of the copper-peptides in the urine producing an aminoaciduria of general nature due to the competition for tubular reabsorption between amino acids and peptides. According to this concept the binding of copper in large amounts is an inherent property of tissues in HLD and is not dependent upon the physical chemical state of copper in the plasma. Consequently, the deposition of copper in tissues is a secondary phenomenon arising from a primary defect in protein metabolism.

The studies reported here were undertaken with the object of determining whether liver tissue in HLD does

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or does not possess a higher affinity to bind ionic copper than does normal liver tissue. Although such a comparative study of fresh liver tissue from patients presents considerable medical and surgical difficulty it was nevertheless undertaken because of the important nature of the information to be gained. Liver tissue was obtained from an asymptomatic case of HLD and from two normal patients. Copper binding by HLD and normal liver tissue was studied both by dialysis equilibrium experiments and by paper electrophoresis, and showed that liver tissue does possess a higher affinity for copper in HLD and that this affinity is localized to a single major electrophoretic component of liver tissue.

Materials and Methods. Approximately 2 gm. of tissue (liver A) were obtained surgically from a 12-year-old boy with hepatosplenomegaly, bilateral Kayser-Fleischer rings, aminoaciduria, peptiduria, and cupruria, but without neurological signs. Histological examination showed severe hepatic cirrhosis. The patient's sister was under study during the same period and presented the classical picture of hepatolenticular degeneration.*

Liver B was obtained surgically from a patient undergoing cholecystotomy for gallstones. Liver C was from a patient undergoing abdominal exploration for gastrointestinal bleeding. Both of these control livers were histologically normal.

Anesthesia used in all cases was cyclopropane-ether.

EQUILIBRIUM DIALYSIS EXPERIMENTS. The liver tissue obtained was immediately frozen with dry ice after small specimens were removed for histological examination. The frozen tissue (about 2.0 gm. each) was weighed, cut into 1 mm. thick sections with a razor blade and homogenized in a Tenbroeck homogenizer with cold 0.15 M sodium acetate-HCl buffer (pH 7.1). The homogenate was filtered rapidly through loosely-packed, acid-washed pyrex glass wool to remove coarse strands of fibrous tissue, and collected in chilled tubes. The homogenates were thoroughly mixed and aliquots removed for nitrogen, phosphorus and copper analyses. The values for these were as follows:

Liver A Homogenate (HLD) per 5 ml.	nitrogen	20.00 mg.
	copper	416 μg.
mg. nitrogen/mg.	phosphorus	9.58
Liver B Homogenate (normal) per 5 ml.	nitrogen	22.35
	copper	67 μg.
mg. nitrogen/mg.	phosphorus	10.38

Only samples of liver A (HLD) and B (normal) were used in these experiments. The procedure used for equilibrium dialysis was essentially that of Klotz *et al.*[10]. Viscose tubing, ¾ inch in diameter, was cut into exactly 6-inch sections and soaked overnight in 0.1% disodium versenate (adjusted to pH 7.1). These were then washed exhaustively for 24 hours with distilled water to remove all traces of versene. Latex surgical gloves dipped in ethanolic rubeanic acid solution[13] and then thoroughly rinsed with distilled water were worn throughout the subsequent handling of the dialysis tubing. The tubing was knotted upon itself and 5.0 ml. of liver homogenate was pipetted into the bags. The second knot was adjusted to exclude air bubbles, and the bags were placed in Erlenmeyer flasks containing 50 ml. of 0.05 M sodium acetate-HCl buffer (pH 7.1). Control flasks contained dialysis bags treated in the same manner but having only 5.0 ml. of the 0.15 M sodium acetate-HCl buffer (pH 7.1) inside. Known amounts of a copper sulfate solution were then added to the solution outside the bags in each Erlenmeyer flask and the system allowed to equilibrate on a rotary shaker in a cold room at 2° C. Aliquots were removed from the outside solution at 24-hour intervals for copper analysis by adaptation of the method of Eden and Green[6] on a micro scale. Further increments of copper in the form of the copper sulfate solution were added to the outside solution at each stage of equilibration together with sufficient buffer to compensate for the volume of aliquots removed. Control systems containing liver homogenate equilibrated against the initial copper solution were run together with the test samples to ascertain stability of the systems over the period during which the experiments were conducted. The diffusible nitrogenous

*A detailed report of clinical and metabolic studies of this family will be presented elsewhere.

constituents of the liver were dialyzed out within 24 hours, so that this nitrogen figure served as the baseline. Increase of nitrogen and copper in the outside solution in these control systems was taken as indicating protein degradation and the experiments were accordingly terminated. Thus the dialysis equilibrium experiments could not be carried on beyond 5 days. The dilution-diffusion effect in the system and the binding of copper by the viscose bags themselves were determined through the estimation of copper in the outside solutions in the control systems. These values were subtracted from the values found for the liver homogenate systems. In this manner, the amount of copper bound by the liver homogenates at each phase of equilibration was calculated. The amount of copper bound by the respective homogenates was referred to the total tissue nitrogen present in the homogenates rather than the original fresh weight of the samples homogenized. The nitrogen to phosphorus ratio of the two homogenates was used to indicate roughly the proportion of nuclear mass versus cytoplasmic mass in each sample.

ELECTROPHORETIC EXPERIMENTS. Sixty milligrams of frozen liver tissue from A, B, and C were homogenized with 0.1 ml. of 0.2 M sodium acetate-HCl buffer (pH 7.1) by grinding with powdered glass in a pyrex microhomogenizer. The homogenates were centrifuged in microcentrifuge tubes at 2000 × gravity for 20 minutes. The extracts of each liver thus obtained were used for the experiments with paper electrophoresis.

The Spinco Model R. Durrum-type paper electrophoresis cell was used for these ex-

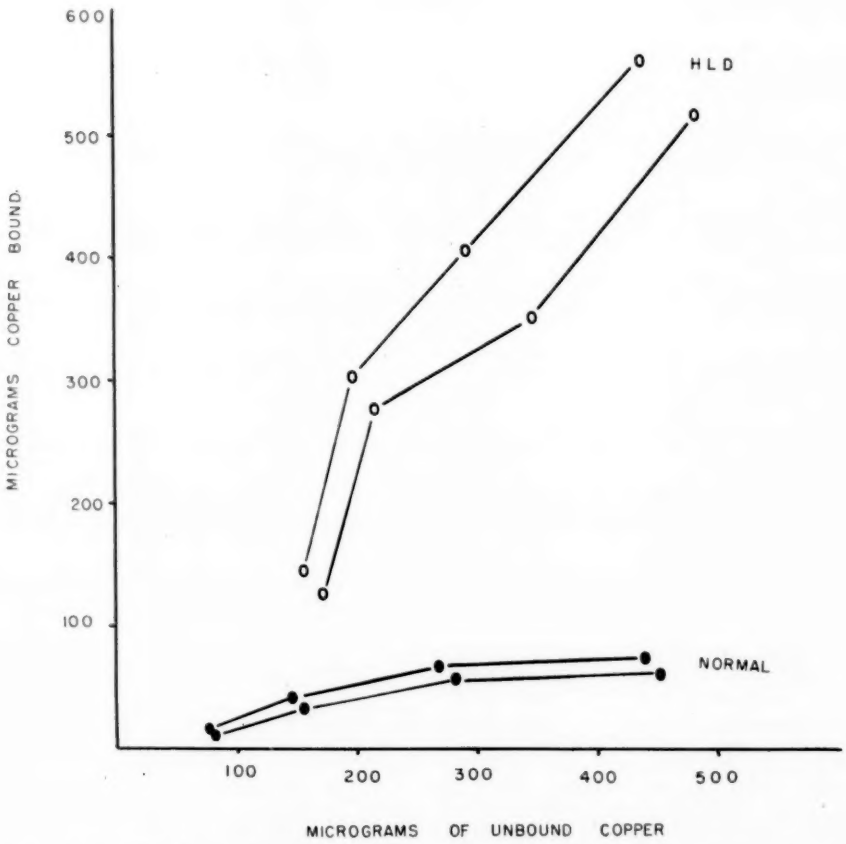

Fig. 1.—The distribution of added copper between liver homogenate and the surrounding solution in a normal and a patient with HLD.

periments. The buffer was 0.025 M ammonium acetate (pH 7.4). Whatman No. 3 MM paper was used throughout, the paper being thoroughly washed with the buffer prior to use, to remove interfering contaminants. The electrical potential difference gradient applied across the paper strips was 17 volts/cm. a 0.5% aqueous solution of sodium diethyldithiocarbamate. Areas containing copper were visualized as intense orange colored bands. The electropherograms thus obtained were scanned with the photoelectric automatic recording scanner of Durrum-Gilford[5] using a 604 mμ filter for ninhydrin-stained strips and

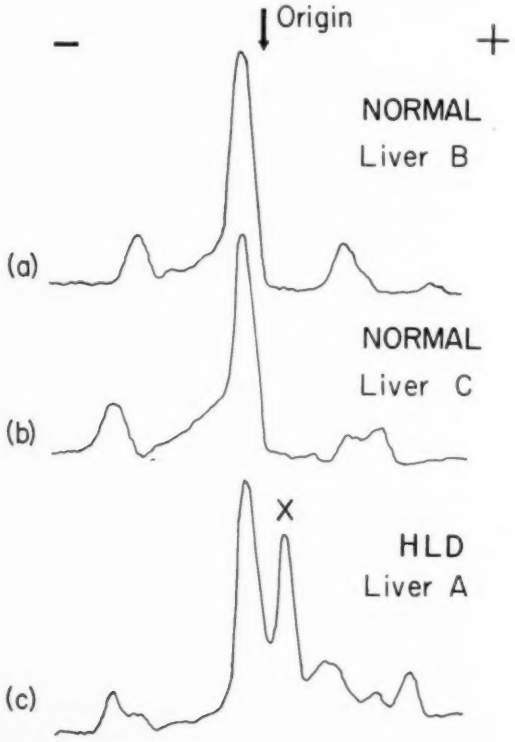

Fig. 2.—Comparison of scanning curves of ninhydrin stained electropherograms of HLD liver (curve c) and two normal livers (curves a and b).

The potential applied between the electrodes was 520 volts, and the time of runs was 80 minutes.

Twenty-five microliters of liver tissue extract from liver A (HLD) was compared with that of livers B and C (normal). After completion of the runs, the strips were dried horizontally in an oven for 5 minutes at 110° C. The ammonium acetate buffer was volatilized during this process. Ninhydrin reacting material was detected by spraying the strips with 0.2% ninhydrin in butanol and heating for 10 minutes in an oven at 110° C. Copper was detected by spraying parallel strips with a 415 mμ filter for the diethyldithiocarbamate stained strips.

Results. Duplicate experiments in which the amount of copper bound by the liver from the patient with HLD was compared with that bound by the normal livers showed increased binding. At a concentration of 4 μg. copper per ml. (200 μg. unbound copper in Fig. 1) the HLD liver had bound twice as much copper as the normal. At a

concentration of 8μg. per ml. (400 μg. unbound copper) the HLD liver had bound five times as much copper as the normal. Thus it is apparent that the liver in HLD possesses a high avidity for copper and that this avidity resides in a nondialyzable fraction presumably protein or polypeptide in nature.

The electrophoretic experiments were designed to compare the electrophoretically distinct fractions of the HLD liver extract with two normal liver extracts in terms of ninhydrin reacting components, copper containing components, and those fractions which might bind additional copper. Thus when 25 μl. of each extract was run under the conditions previously described, the two normal liver extracts showed essentially similar ninhydrin reacting patterns while the HLD liver possessed a different pattern (Fig. 2). Qualitatively the most important difference was represented by an additional slow-moving band migrating toward the anode (Fig. 2, Peak X). The color of this band was an intense blue in contrast to the purple of the other bands. When parallel strips of the 3 extracts were stained for copper with diethyldithiocarbamate, no copper could be detected on the two normal liver electropherograms as the amount

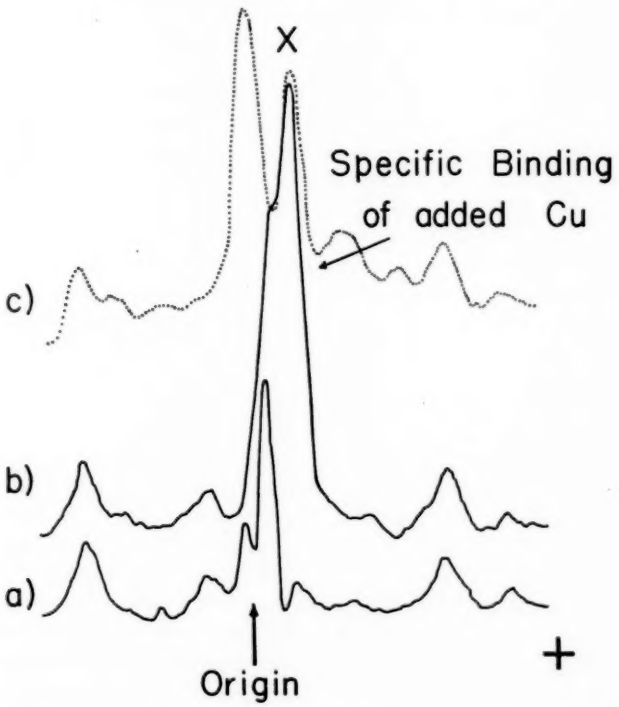

Fig. 3.—Localization of copper density areas. The localization of copper on copper stained HLD electropherogram (curve a) is compared with a ninhydrin stained HLD electropherogram (curve c). Copper added to the system is specifically bound by components of the X-peak (curve b, copper stain).

present was below the sensitivity range of the reagent. The HLD liver electropherogram showed many bands of copper density (Fig. 3a) with the highest copper density occurring at a site corresponding to a slow-moving component of the X-band detected with ninhydrin (compare with Fig. 3c). Were all of the components of the X-band saturated with copper, the shape of the 3a curve would be expected to coincide with that of the X-band.

When 25 μl. of liver extracts of A, B, and C were placed at the point of origin together with 15 μl. of a copper sulfate solution containing a total of 1.5 μg. of copper and the electropherograms obtained after a run under the conditions described were stained for copper, the normal liver electropherograms (livers B and C) showed no detectable copper, the copper ions having rapidly moved off the paper. The HLD electropherogram on the other hand showed the fixation of all the copper in a zone corresponding to the band X of the ninhydrin stained electropherogram (Fig. 3, curve b) with an accentuation of the copper peak originally present, but without increase in copper density in the other copper containing bands (compare tracings a and b, Fig. 3). Thus band X, which distinguishes the HLD ninhydrin electropherogram from the normal electropherogram, also possesses a specific copper binding capacity not shared by the other electrophoretically distinguishable fractions of HLD liver as well as those of normal liver.*

Discussion. The observations presented here are amenable to interpretation only if the two assumptions which are implicit in this study are valid, that is, (a) that the binding of copper to tissue is not enzyme mediated, and (b) that the copper bound by tissue components is in ionic form at the instant of binding irrespective of its state just prior to binding. Since all present evidence supports these two assumptions and since both of the hypotheses concerning the pathogenesis of HLD are based on their validity, the observations presented here may be interpreted as indicating an abnormal avidity for copper inherently present in the protein or polypeptide constituents of the liver in hepatolenticular degeneration.

Until the X-band fraction is isolated and studied, nothing can be said about the nature of the structural abnormality in the liver proteins in HLD. The significant point at present is the magnitude of the affinity for copper that the HLD liver shows and the rather specific component to which added copper is firmly attached. Bearn and Kunkel[1,2], and Matthews[11] have presented data showing that intravenously and orally administered copper-64 disappears less rapidly from the plasma in HLD when compared to normals, and that the formation of ceruloplasmin is markedly impaired. Their observations are compatible with the data in this paper because they are measuring rate of exchange of copper-64 with stable tissue copper, rather than disappearance of copper from the blood stream. Gubler *et al.*[7] were unable to demonstrate any rise in plasma copper even after massive oral doses were administered. In view of the tight binding that occurs between ionic copper and liver tissue in HLD, the exchange of copper-64 with bound copper would occur more slowly, and be manifest by a slower rate of removal of copper-64 from plasma. Under such conditions more of

*After this manuscript was submitted, the authors had the opportunity of studying surgically removed cirrhotic liver tissue under similar conditions. The electrophoretic pattern obtained was similar to those of the normals presented here.

the copper-64 might then be expected to appear in the urine, although this cannot be construed as the reason for the cupruria observed in this disease inasmuch as a very small percentage of the total administered copper-64 was demonstrated in the urine[11]. The deficiency of ceruloplasmin in this disease[12] would likewise find explanation in the firm binding of available copper to liver proteins (stable to an electrical field generated by 520 volts). Thus it can be assumed that the "apoceruloplasmin" synthesized is not given any copper necessary for its enzymatic[8,9] and chemical identity, or that the excess copper bound by the HLD liver blocks the ceruloplasmin synthesizing systems of the organ. Besides these considerations, however, a conclusion of greater importance suggests itself. It would be deemed unlikely that a genetically determined difference in protein copper affinity should be limited to liver proteins alone. Extension of this concept to other organs would not only explain copper deposition in different parts of the body, but more significantly, would explain the nature of intestinal over-absorption of dietary copper in this disease[1,3,4,11]. Increased absorption of ingested copper would thus be an expression of increased copper binding capacity of the intestinal mucosa. Thus, we suggest that the conclusion offered by our observations can be logically extended to explain the intestinal over-absorption of copper in HLD and conclude that this avenue would be worthy of future exploration.

Summary. Dialysis equilibrium experiments using surgically removed liver tissue homogenates from a selected early case of hepatolenticular degeneration (HLD) and a normal subject showed a markedly increased avidity for copper in the former.

Electrophoretic experiments comparing the liver extract of the HLD patient with that of two normal subjects showed a qualitative difference in electrophoretically distinct fractions indicating the presence of an extra fraction in the liver in HLD. The increased copper avidity of the HLD liver was shown to be specifically due to the high copper binding properties of this fraction. It is concluded that the mechanism of copper deposition in the liver in HLD is due to a genetically determined abnormality in protein metaboolism leading to the formation of proteins with high copper avidity. It is suggested that the intestinal over-absorption of copper is due to the same mechanism.

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SUMMARIO IN INTERLINGUA

Le Mechanismo del Deposition Cuprose in le Hepate in Degeneration Hepatolenticular (Morbo de Wilson)

Experimentos a equilibrio dialytic, executate con homogeneatos de histos hepatic obtenite per ablation chirurgic ab un selegite caso de degeneration hepatolenticular initial e ab un subjecto normal, monstrava un marcate augmento del aviditate pro cupro in le prime.

Experimentos electrophoretic, comparante le extracto hepatic del patiente de degeneration hepatolenticular con le extracto hepatic de duo subjectos normal, monstrava un differentia qualitative de electrophoreticamente distincte fractiones: un fraction additional se trovava in le hepate del patiente de degeneration hepatolenticular. Il esseva demonstrate que le augmento del aviditate pro cupro in le hepate del patiente de degeneration hepatolenticular resultava specificamente del alte potentia cupro-ligante del fraction additional. Nos conclude que le mechanismo del deposition cuprose in le hepate de patientes con degeneration hepatolenticular resulta de un geneticamente determinate anormalitate del metabolismo proteinic que produce proteinas con forte aviditate pro cupro. Es postulate que le hyper-absorption intestinal de cupro resulta del mesme mechanismo.

SUMMARIO IN INTERLINGUA

(See page 502 for original article)

Observatione Electrocardiographic in Patientes con Accidentes Cerebrovascular Reporto de 12 Casos

Ben que anormalitates electrocardiographic associate con accidentes cerebrovascular habeva essite observate in le passato, iste alterationes esseva describite in detalio solmente in publicationes de datas relativemente recente. Le hic reportate 12 patientes con varie accidentes cerebrovascular, principalmente hemorrhagias subarachnoide, exhibiva prolongation del intervallo QT e anormalmente large e frequentemente invertite undas T (undas T–U). Il habeva in nostre casos nulle apparente correlation inter le anormalitates electrocardiographic e le electrolytos del sero, le temperatura corporee, o le pression del sanguine. Al tempore presente, causas exacte de iste constatationes electrocardiographic non es definitemente cognoscite. Nos discute le varie factores que es possibilemente involvite in le production del alterationes in question..

THE PROBLEM OF ESTABLISHED ATRIAL FIBRILLATION

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Since it has been reported that atrial fibrillation can be converted to normal sinus rhythm without the great dangers previously thought to exist[11,16,23,26,30,41], the condition has become a greater therapeutic challenge.

The purpose of this paper is to review the problem briefly and to make recommendations as to which patients should be considered candidates for conversion to normal rhythm. The advantages to be gained by the establishment of normal sinus rhythm and the dangers, particularly as related to quinidine toxicity, will be discussed. A series of 30 cases who were given quinidine in an effort to establish normal rhythm will be reported.

During physiological observation of animals, it was noted that atrial fibrillation produced functional impairment of the heart[19,34,35] and after normal rhythm was restored improvement occurred[34]. In patients with atrial fibrillation the cardiac output was found to be below normal despite control of the heart rate with digitalis, and after conversion to normal rhythm, the cardiac output usually increased either at rest or following exercise[12,15,17].

Clinical studies have shown increase in blood flow as measured by the circulation time after establishment of normal rhythm[3]. The heart rate was greater after exercise of patients with atrial fibrillation than those with normal rhythm and the return to normal more prolonged even in patients adequately digitalized[4]. Patients with atrial fibrillation who are in intractable heart failure despite digitalization, restriction of sodium and the administration of mercurial diuretics have been restored to compensation after the establishment of normal rhythm[30]. Atrial fibrillation may be followed by increase in heart size and congestive failure in individuals who have no other evidence of heart disease even when the rate is controlled with digitalis[26].

Embolic phenomena frequently occur in patients with atrial fibrillation. It has been reported that this arrhythmia was present in 90% of 194 patients with rheumatic heart disease who had peripheral emboli[6]. Emboli were the cause of death in approximately 10 to 20% of patients with rheumatic heart disease[8,20,38]. Sudden death is more common in cardiac patients with atrial

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fibrillation than in those with normal rhythm[1,30].

There are, therefore, good reasons to attempt to convert patients with atrial fibrillation to normal rhythm, but the dangers which accompany the conversion must be weighed against the advantages to be gained. The dangers are due to the change from atrial fibrillation to normal rhythm and to the toxicity of the drugs used to effect conversion.

The danger due to the change from atrial fibrillation to normal rhythm is that of embolization at the time of, or shortly after, sinus rhythm develops. This has recently been minimized, but the actual incidence is not known. There are a number of series reported in which the establishment of normal rhythm was accomplished without the development of any emboli[23,25,26,30]. Goldman[11] reported three instances of probable embolism shortly after sinus rhythm was established in a series of 67 patients. However, one of these patients had had previous emboli and it is difficult to be sure whether the emboli resulted from restoration to normal rhythm or would have occurred anyway. Hay[14] reported seven instances of peripheral embolism following 156 successful conversions to normal sinus rhythm.

Quinidine is most frequently employed to effect conversion, although Pronestyl has been used also[22,24,27]. Similar toxic effects may be produced by these two drugs. These include gastrointestinal manifestations, central nervous system reactions, respiratory failure, blood dyscrasias, drug fever, skin eruptions, and, of particular importance, various arrhythmias and conduction system abnormalities[2]. Atrial flutter with increase in ventricular rate, nodal rhythm, ventricular ectopic beats, and ventricular fibrillation have been reported following their administration[2,30]. Both decrease conduction velocity with resultant widening of the QRS complexes[28] and increase of the PR interval. Both drugs have a vagolytic effect and also decrease peripheral resistance with a resulting drop in blood pressure[2]. Cardiac failure may occasionally be made worse by quinidine[30] and cardiac standstill has been reported as a result of its use[1,30]. Quinidine and Pronestyl most likely produce their therapeutic effect in atrial fibrillation by depressing the excitability of the ectopic focus in the atrium so that the sinus node may resume its function[28].

It is probable that the effect of quinidine depends on its plasma concentration though there is considerable variation in the level at which conversion to sinus rhythm occurs[21,28]. Sokolow[30] reported that, in 93 successfully treated patients, the plasma quinidine level averaged 5.4 mg. per L. at the time normal rhythm developed. If conversion did not occur at levels below 9 to 10 mg. per L., it was unlikely to occur at higher levels. He also found that serious toxicity is infrequent at levels of 6 to 8 mg. per L., but that this possibility increased with levels of 9 to 10 mg. per L. Quantitative determination should be done, if possible about 2 hours after the last dose of the drug is given, so as to be sure that adequate therapeutic levels are attained and toxic levels not reached.

THE PROBABILITY OF SUCCESS OF CONVERSION. Bellet[2] states that 50 to 85% of patients with atrial fibrillation can be converted to normal sinus rhythm and that 25% will remain converted. Normal sinus rhythm may be obtained in patients with all types of heart disease, in long standing atrial fibrillation and chronic heart failure. Some reports, however, indicate that conversion is more difficult when atrial fibrillation is associated with rheumatic heart dis-

ease[11,16,36]. There are others which show a similar incidence of conversion in this and other types of heart disease[37,40], and in one report patients with rheumatic heart disease were more easily restored to normal sinus rhythm than those with other types[41]. The incidence of successful conversion has also been reported to be lower in patients with enlarged hearts and severe heart failure[16,26,37], but there are other reports indicating that these factors did not seem to be important in affecting the chances of conversion[11,23,41].

One of the problems in the management of atrial fibrillation is the incidence of relapse. This probably depends not only on the continuous administration of quinidine, but also on the age of the patient and the underlying heart disease. Patients who receive adequate maintenance doses of quinidine are less apt to relapse than those who do not[10,13,25,30]. Relapse is more common in patients over 50 years of age[26] and in those with severe heart failure[37]. It is also reported to be more frequent in degenerative than in rheumatic heart disease[23].

Methods and Materials. An attempt was made to convert 30 patients with atrial fibrillation to sinus rhythm and it is with these that this report primarily deals. They were admitted to the Medical Service of the Chesapeake and Ohio Hospital, Clifton Forge, Virginia, or to the Medical Service of the University of Virginia Hospital. They were classified as follows: 1) degenerative heart disease, including arteriosclerotic and hypertensive heart disease; 2) rheumatic heart disease; 3) thyroid heart disease; 4) chronic cor pulmonale; 5) atrial fibrillation without obvious heart disease.

All patients were digitalized prior to the attempt, in order to decrease the ventricular rate and to control heart failure when it existed. Since atrial flutter is a frequent occurrence during the conversion of atrial fibrillation to normal rhythm[9,11,28,30,39], the depression of AV conduction produced by digitalis was considered to be a safeguard against the occurrence of a rapid ventricular rate resulting from the appearance of 1:1 or 2:1 flutter.

TABLE 1.—QUINIDINE DOSE SCHEDULE AND ESTIMATED PLASMA LEVELS

Day	*Indiridual Dose* gm.	*Total Dose* gm.	*Estimated Residual Concentration from Previous Day* mg./L.	*Estimated Net Peak Level* mg./L.	*Estimated Total Peak Level* mg./L.
1.	0.2 gm. q2h × 5	1.0	0	3.9	3.9
2.	0.3 gm. q2h × 5	1.5	1.64	4.4	6.04
3.	0.4 gm. q2h × 5	2.0	2.54	4.9	7.44
4.	0.5 gm. q2h × 5	2.5	3.12	5.3	8.42
5.	0.6 gm. q2h × 5	3.0	3.54	5.7	9.24
6.	0.7 gm. q2h × 5	3.5	3.86	6.1	9.98
7.	0.8 gm. q2h × 5	4.0	4.2	6.5	10.5
8.	0.9 gm. q2h × 5	4.5	4.4	6.9	11.3
9.	1.0 gm. q2h × 5	5.0	4.75	7.3	12.05

An anticoagulant, Dicumarol or Tromexan, was given to most of the patients for 10 to 14 days prior to the administration of quinidine in an effort to prevent embolization. It was postulated that a newly formed thrombus should have became adherent in that time and the anticoagulant would prevent the development of fresh thrombi so that when normal atrial contraction occurred embolization would not follow. Anticoagulants were also used in the studies of Goldman[11] and Sokolow[30].

Quinidine was administered to all patients according to the dose schedule suggested by Sokolow, which allows approximate estimation of plasma quinidine levels[31]. He found that the average peak quinidine level occurs 2 hours after a particular dose is given, and that the average residual level 12 to 18 hours after the last dose is 42% of the peak level. Table 1 gives the schedule of administration of quinidine showing the individual and total daily dose, the estimated residual quinidine level and the predicted peak plasma quinidine

level. The latter was obtained by adding the predicted peak level produced by a particular dose to the estimated residual level from the previous day. Extrapolations were made when the estimated peak level was not known. This schedule was not strictly followed, the dose often being increased by 0.2 gm. instead of 0.1 gm., or in some patients being maintained at the same level for 2 or 3 consecutive days. This resulted, of course, in variation of the estimated peak levels.

TABLE 2.—REASON FOR CONVERSION

	No.	*%*
Heart failure alone	9	30.0
Heart failure and emboli	16	53.4
Heart failure and angina	2	6.6
Emboli alone	2	6.6
Atrial fibrillation alone	1	3.4
Total	30	100.0

The schedule was interrupted when sinus rhythm was established, following which 0.2 to 0.4 gm. of quinidine were given q.i.d. An additional 0.2 to 0.4 gm. of an enteric coated capsule was given at bedtime to several patients. If toxicity developed or if conversion did not occur after 5.0 gm. were given in one day, the attempt was abandoned.

The apical rate was counted and the rhythm determined by a physician before each dose was given. An electrocardiogram was usually taken daily before the drug was begun and 2 hours after the last dose or whenever a change in rhythm was noted. On several occasions normal rhythm was resumed during the night after the peak level had passed. The occurrence of nausea, vomiting, diarrhea, or tinnitus was considered to indicate mild toxicity and the drug was not stopped, although the patient was carefully observed. The occurrence of an increase in intraventricular conduction time of more than 25%, or the appearance of ventricular ectopic beats, ventricular tachycardia, or nodal rhythm was considered to indicate serious toxicity and the drug was discontinued.

Results. REASONS FOR CONVERSION. Table 2 shows the reasons for conversion. Nine patients had heart failure alone. In 16 patients heart failure and a history of embolic phenomena existed. In 2 patients heart failure and angina were present. Two had emboli only, and, in one, the only reason for conversion was the presence of atrial fibrillation.

Table 3 shows a summary of the results.

Total successes were defined as patients who were converted and who remained in normal sinus rhythm for 2 weeks or longer. Most of those who relapsed after 2 weeks had either reduced the quinidine or stopped it altogether.

It can be seen that 21 of 30 patients, or 70%, were converted, but that 6 of these relapsed within 2 weeks, so that there were 15 total successes, or 50%.

The incidence of conversion in the degenerative heart disease group was higher than that attained in the rheumatic group, although, because of the small number of patients involved, definite conclusions cannot be drawn.

TABLE 3.—RESULTS

Type	*No.*	*No. Converted*	*%*	*No. Relapsed*	*%*	*No. Not Converted*	*%*	*No. Successes*	*%*	*No. Failures*	*%*
Deg.	14	11	78.6	3	27.3	3	21.4	8	57.0	6	43.0
Rheu.	11	7	63.6	3	42.8	4	36.3	4	36.3	7	63.7
Cor P.	1	0	0	0	0	1	100.0	0	0	1	100.0
Thyroid	1	1	100.0	0	0	0	0	1	1.0	0	100.0
None	3	2	66.6	0	0	1	33.3	2	66.6	1	33.3
Total	30	21	70.0	6	28.6	9	30.0	15	50.0	15	50.0

EMBOLIC PHENOMENA. In Table 4 it is seen that 16 emboli occurred in 9 patients before conversion and that none occurred during or immediately after normal rhythm was established. One patient had 9 emboli during the 3 years before she was converted, while none occurred during the 2 years following conversion.

HEART FAILURE. Table 5 shows the effect of conversion on heart failure. Of the 12 patients with heart failure who were successfully converted, all improved after normal rhythm was restored and in several this improvement was dramatic.

TABLE 4.—EMBOLIC PHENOMENA

	Successes		
Type	*No. Pts.*	*No. Emboli*	*No. During and After Conversion*
Deg.	5	5	0
Rheu.	3	11	0
Cor P.	0	0	0
Thyroid	0	0	0
None	1	0	0
Total	9	16	

HEART SIZE. The heart size was determined by orthodiagram or teleoroentgenogram in 18 patients before and after the attempt to convert was made and Table 6 shows these results. The heart size is expressed as percentage of the transverse diameter of the frontal plane above the predicted normal, according to Kurtz[18] and to Ungerleider[36]. It can be seen that all of those measured showed a decrease in heart size when restoration to normal rhythm was accomplished. There was an average decrease from +31.3% to +22.5%.

However, of those patients who were not converted, only one showed a significant decrease in heart size, and, in fact, there was an average increase of from +25.3% to +28.2%.

In one patient the stroke volume and cardiac output were estimated by the Starr formula[32,33] before conversion was attempted and repeated after normal rhythm had been restored. Prior to conversion the stroke volume was 58 ml. and cardiac ouput 3750 ml. per minute, while after the establishment of normal sinus rhythm the stroke volume had increased to 68 ml. and the cardiac output to 4375 ml. per minute. This patient had been in failure, but was compensated at the time of conversion.

Atrial flutter was found in ten instances during the process of conversion and it is probable that it was more

TABLE 5.—HEART FAILURE

Type	*No.*	*Successes*	*%*	*Improved*	*%*	*Unimproved*	*%*
Deg.	14	7	50.0	7	100	0	0
Rheu.	11	4	36.4	4	100	0	0
Cor P.	1	0	0	0	0	0	0
Thyroid	1	1	100.0	1	100	0	0
None	0	0		0		0	
Total	27	12		12		0	

TABLE 6.—HEART SIZE, TRANSVERSE DIAMETER

	Successes			*Failures*	
Case	*Before Conversion*	*After Conversion*	*Case*	*Before Attempt*	*After Attempt*
B_1	30	25	C_1	32	33
B_2	20	7	S_1	52	38
B_3	30	20	S_2	42	48
E	34	32	S_3	45	44
S	18	12	T	32	45
P	26	22	C_2	8	18
L	45	37	J_1	6	6
M	52	38	J_2	6	12
H	28	10	W	5	10
Average	31.3	22.5		25.3	28.2

frequent than found. Figure 1 shows an example of this phenomenon.

DOSE OF QUINIDINE REQUIRED TO EFFECT CONVERSION. Table 7 shows the doses of quinidine given to those converted, as well as the estimated plasma level attained. It is striking that all of the 3 patients who required 4 gm. in one day to effect conversion relapsed within 2 weeks and that three of five who required 3.0 gm. for conversion relapsed. The percentage of successful conversions was excellent if this could be done with 2.5 gm. or less of quinidine in one day.

Table 8 shows the doses given to patients who did not convert. In all these "unsuccessfully treated patients" toxicity developed in all but one, a patient who did not convert after 5.0 gm. were given in one day, further increase being thought to be unwise and useless.

TOXICITY TO QUINIDINE. In Table 7 are shown the types of reaction to

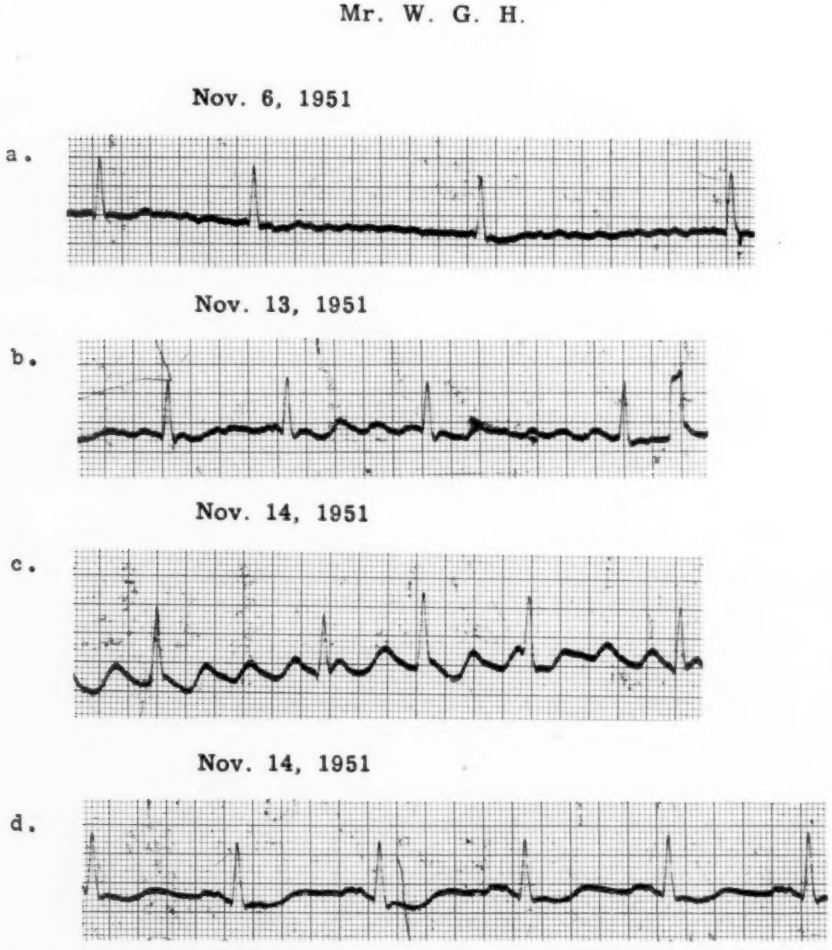


Fig. 1.—*a*) Before conversion, showing atrial fibrillation with fast atrial rate; *b*) during conversion, showing atrial fibrillation with slow atrial rate; *c*) during conversion, showing atrial flutter; *d*) after conversion.

quinidine which occurred and the number of times each was noted.

Marked generalized weakness was noted eight times, but in none was it severe enough to warrant stopping the drug.

Gastrointestinal upsets occurred six times and in one instance, necessitated discontinuing the drug. This patient received 0.6 gm. every 2 hours for five doses (3.0 gm.), producing an estimated quinidine level of 9.1 mg. per L.

Ventricular ectopic beats occurred six times and in 3 patients the drug was stopped because of them.

Ventricular tachycardia was found twice and in one patient ventricular fibrillation and nodal rhythm occurred (Fig. 2).

Figure 3 shows the electrocardiogram of a patient who had runs of ventricular ectopic beats without symptoms.

Syncope occurred in a patient who was found to have ectopic ventricular beats alternating with normal beats and it is presumed that either asystole or ventricular fibrillation occurred which produced the cerebral ischemia causing syncope. The drug was discontinued and the following day normal rhythm was present (Fig. 4).

FOLLOW-UP. The 15 patients who were successfully converted were followed from one month to 4 years and Table 9 shows the number who were known to remain in normal rhythm at intervals following conversion. Only two were followed for 2 years or more and both were improved. One who had repeated emboli prior to conversion has had none since. The same patient was in severe congestive failure poorly controlled by digitalis, sodium restriction, diuretics, and cation exchange resins before conversion, but improved and remained so for 18 months. Then failure again became uncontrollable and mitral valvuloplasty was performed with dramatic improvement.

TABLE 7.—PATIENTS CONVERTED

Quinidine Dose		*Total*	*No. Pts.*	*No. Remained Converted*	*Estimated Quinidine Level mg./L.*
0.8	q2h × 5	4.0	3	0	10.1
0.6	q2h × 5	3.0	5	3	9.1
0.5	q2h × 5	2.5	2	2	8.4
0.4	q2h × 5	2.0	5	5	7.4
0.3	q2h × 5	1.5	2	2	6.0
0.2	q2h × 5	1.0	4	3	3.9
		Total	21	15	

TABLE 8.—PATIENTS NOT CONVERTED

Quinidine Dose		*Total*	*No. Pts.*	*Estimated Quinidine Level mg./L.*
1.0	q2h × 5	5.0	1	10.8
0.6	q2h × 5	3.0	4	9.1
0.4	q2h × 5	2.0	3	7.4
0.2	q2h × 5	1.0	1	3.9
		Total	9	

Discussion. It appears that atrial fibrillation *per se* is potentially dangerous since it may be a major factor in precipitating or abetting heart failure, it predisposes to embolization, and it may be associated with sudden death. It has been shown that correction of atrial fibrillation will be followed by

Miss B. S.

May 7, 1953

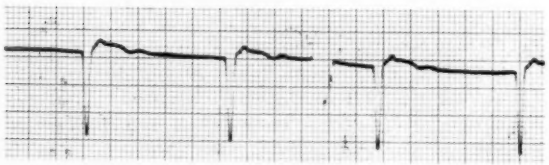
a.

May 8, 1953

b.

May 8, 1953

b.



May 8, 1953

c.

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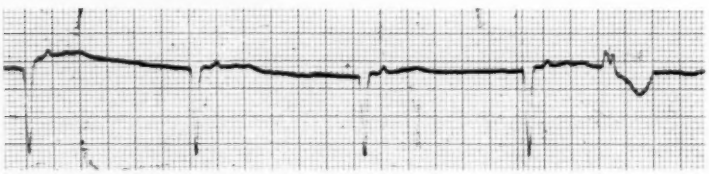

May 8, 1953

May 9, 1953

d.

e.

Fig. 2.

(Legend on opposite page)

increase in cardiac output, improvement in heart failure, and cessation of embolic episodes.

The results of the present report seem to support these findings. Heart size decreased, heart failure improved, and no further emboli occurred in patients successfully converted.

The development of frequent ectopic beats in 6 patients, the occurrence of ventricular tachycardia in two and transient ventricular fibrillation in one of these is disturbing. One patient who had received a total of 2.0 gm. in 24 hours with an estimated blood level of 7.4 mg. per L. was found to have runs of ventricular ectopic beats by routine electrocardiogram, although he had no symptoms referable to the arrhythmia. Another patient developed frequent

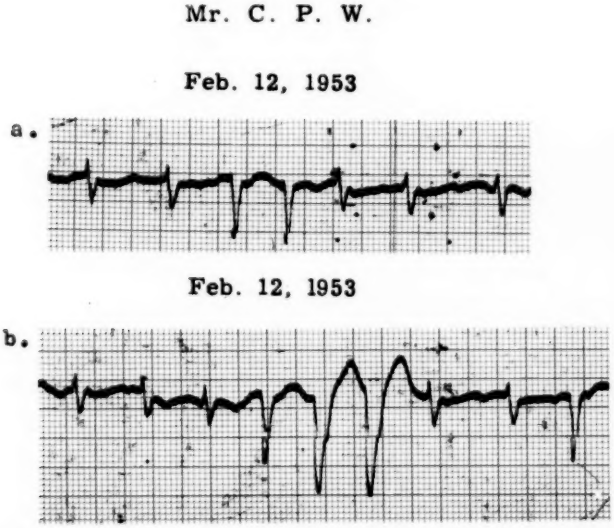

Fig. 3.—Electrocardiograms of a 61-year-old man, Mr. C.P.W., who had arteriosclerotic heart disease with atrial fibrillation, congestive failure, and left hemiplegia presumably from an embolus. Digitalization had been carried out prior to admission to the hospital. Tromexan was given for 10 days and following this quinidine was administered in increasing amounts until a dose of 0.4 gm. every 2 hours five times (2.0 gm.) was reached. He had no symptoms, but an electrocardiogram showed runs of ventricular ectopic beats (*b* & *c*). Because of the potential danger of this arrhythmia the drug was discontinued.

Fig. 2.—Electrocardiograms of a 65-year-old woman, Miss B.S., a known hypertensive who developed left hemiparesis and on admission to the hospital was found to have atrial fibrillation. Digitalization was carried out and following this electrocardiogram (*a*) was taken. She was given Tromexan for 9 days and then quinidine was administered in increasing doses until she had received 0.6 gm. every 2 hours for five doses (3 gm.). Since normal rhythm was not restored, the same dose was given the following day. Eight hours after the last dose she became unconscious, had a convulsion, and respiration ceased. Following artificial respiration for approximately one minute, spontaneous respirations resumed. An electrocardiogram showed nodal rhythm with ventricular ectopic beats (*b*). Five hours later a second convulsion occurred and following this the electrocardiogram showed nodal rhythm, ventricular ectopic beats, and a burst of ventricular tachycardia with wide complexes resembling ventricular fibrillation (*c*). Then there was resumption of normal rhythm (*d*). Quinidine was not begun again and consequently atrial fibrillation recurred (*e*).

ventricular ectopic beats associated with syncope probably due to ventricular standstill or ventricular fibrillation, although he had received an even smaller dose. A third patient developed nodal rhythm, ventricular ectopic beats and probable ventricular fibrillation associated with syncope and convulsions. The estimated plasma quinidine concentration of this patient was between 9 and 10 mg. per L. All of these patients had severe heart disease which may be a contributing factor to the quinidine toxicity.

It would be interesting to know what the measured plasma quinidine concentration was at the time these arrhythmias occurred. It is possible that it was higher than estimated, and, had the plasma concentration been determined

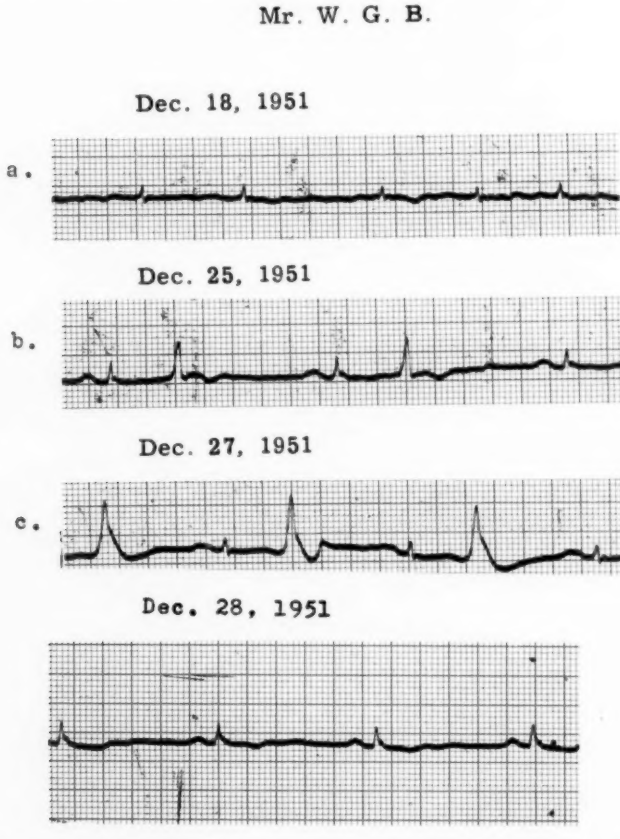

Fig. 4.—Electrocardiograms of a 61-year-old man, Mr. W.G.B., who had arteriosclerotic heart disease, angina pectoris, congestive failure, and atrial fibrillation with a ventricular rate of 135 per minute. He was digitalized and the electrocardiogram which was taken following this is shown in (*a*). After he was given Dicumarol for 12 days, quinidine was administered in doses of 0.2 gm. every 2 hours five times (1.0 gm.). The next day, ventricular ectopic beats alternating with normal beats were found in (*b*). Quinidine was then given 0.2 gm. four times a day and the following morning normal rhythm was present. However, in the afternoon he developed syncope with incontinence and apnea lasting for 30 to 60 sec. Following spontaneous recovery, bigeminy was found again (*c*). The quinidine was discontinued, normal rhythm followed and remained for at least 18 months.

and found above 9 to 10 mg. per L., the drug might have been discontinued prior to the development of arrhythmias. This seems to support the view that plasma quinidine concentration should be determined frequently during the conversion of atrial fibrillation

TABLE 9.—TOXIC EFFECTS OF QUINIDINE

Reaction	*No. Times Occurred*
Weakness	8
G.I. upset	6
Vertigo	4
Frequent ventricular ectopic beats	6
Ventricular tachycardia	2
Ventricular fibrillation	1
Increase in heart failure	2
Marked increase in QRS	1
Tinnitus	1

TABLE 10.—FOLLOW-UP OF CONVERTED PATIENTS

Number who remained in NSR for						1 month	14
"	"	"	"	"	"	2 months	9
"	"	"	"	"	"	6 months	6
"	"	"	"	"	"	1 year	4
"	"	"	"	"	"	18 months	4
"	"	"	"	"	"	2 years	2

to normal rhythm, particularly in older patients with severe heart disease[30]. Because of quinidine toxicity, careful selection of patients should be made and the indications for therapy should be clear-cut.

It seems imperative to emphasize that patients who are candidates for conversion should be under constant observation in a hospital, that they should be seen by a physician before each dose of quinidine is given, and that electrocardiograms should be taken frequently. If arrhythmias occur or if the intraventricular conduction time increases more than 25%, the drug should be discontinued.

It is suggested that the following patients who have atrial fibrillation should be considered candidates for conversion:

1) Patients with a history of embolic episodes. 2) Patients with heart failure not satisfactorily controlled with digitalis, sodium restriction, and diuretics. 3) Patients with recently acquired atrial fibrillation. 4) Patients without other evidence of heart disease who give a history of embolic episodes and who have heart failure or cardiac enlargement.

It is further suggested that the following patients not be subjected to quinidine therapy in an attempt to establish normal rhythm. 1) Patients with failure well controlled by digitalis and sodium restriction, particularly elderly individuals. 2) Patients with atrial fibrillation without other evidence of heart disease who have had the arrhythmia for a year or more and who do not give a history of embolic episodes, heart failure or cardiac enlargement. The heart rate, however, should be kept within a satisfactory range with digitalis. It has been reported that such patients who do not develop failure within one year are not likely to do so[26].

Summary. 1. The pathological physiology of atrial fibrillation has been reviewed and the changes brought about by conversion to normal rhythm summarized.

2. Thirty cases are reported on whom attempts at conversion were made; 15 of these were considered to be successful.

3. The danger of quinidine toxicity is emphasized and three incidences of serious toxicity are reported. Two of these patients had been given small doses.

4. Recommendations are made as to selection of patients for attempted conversion to normal rhythm.

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SUMMARIO IN INTERLINGUA

Le Problema de Establite Fibrillation Atrial

1. Le physiologia pathologic de fibrillation atrial es revidite, e le alterationes effectuate per conversion a rhythmo normal es summarisate.

2. Es reportate le casos de 30 patientes in qui le tentativa a effectuar conversion esseva interprendite. In 15 de iste casos le resultato esseva considerate como un successo.

3. Es signalate le periculo de toxicitate quinidinic. Tres occurrentias de sever toxicitate es reportate. Duo de iste patientes habeva recipite parve doses.

4. Es presentate recommendationes relative al selection del patientes in qui le conversion a rhythmos normal es a tentar se.

STUDY ON THE EFFECT OF OVERDOSES OF PENTYLENETETRAZOL AND BARBITURATE COMBINATIONS IN HUMAN VOLUNTEERS

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In a previous study[7] it was shown that the ingestion of large doses of pentylenetetrazol and pentobarbital sodium combinations delayed the onset of sleep and produced no untoward effects. Six subjects were used in that study, and the total dose of pentylenetetrazol varied from 3,000 to 3,600 mg. and that of pentobarbital sodium from 1,000 to 1,200 mg. In each case, the amount of pentylenetetrazol was three times that of the barbiturate. It was further shown that the addition of pentylenetetrazol to the barbiturate in the usual therapeutic doses did not interfere with the hypnotic and sedative effects of the latter.

In a subsequent study[1] on 10 volunteers, it was demonstrated that pentylenetetrazol (up to 6,000 mg.), when incorporated in a definite proportion of 3 to 1 with pentobarbital sodium (up to 2,000 mg.), afforded significant protection against the depressant effects of the latter. The maximum doses of both drugs were of the magnitude usually held to produce severe poisoning in humans. Nausea and vomiting occurred in 7 of the 10 subjects. Frank convulsions or anesthesia were not observed.

The present investigation is a comparative study to determine (a) the relative human toxicities of combinations of pentylenetetrazol with pentobarbital sodium, secobarbital sodium, and phenobarbital sodium, respectively; (b) the duration of action of these combinations as evidenced by clinical signs and blood levels; and (c) the protective effect afforded by pentylenetetrazol in these combinations. In addition, large doses of pentobarbital sodium alone were administered to a control group of volunteers to illustrate more clearly the magnitude of the protective effect of pentylenetetrazol when taken simultaneously with barbiturates.

Methods. Adult healthy male volunteers in post-absorptive state were given fixed mixtures of pentylenetetrazol and barbiturates in single doses as follows: (A) Ten subjects in-

gested 1,300 to 2,000 mg. of pentobarbital sodium and 3,900 to 6,000 mg. of pentylenetetrazol; (B) six ingested from 1,300 to 1,500 mg. of secobarbital sodium and 3,900 to 4,500 mg. of pentylenetrazol; (C) nine ingested 2,000 to 4,100 mg. of phenobarbital sodium and 3,000 to 6,150 mg. of pentylenetetrazol. A control group of 6 subjects were given 800 to 1,000 mg. of pentobarbital sodium without pentylenetetrazol.

Extreme care was taken that each subject swallowed and retained the entire dose which was completely ingested within one minute. The subjects were kept under constant observation for at least 48 hours following ingestion. Blood was drawn at various intervals and barbiturate levels were estimated by the ultraviolet spectrophotometric method of Goldbaum[5].

Results. The results of this study are embodied in Tables 1, 2, 3, 4, and Fig. 1.

A. PENTOBARBITAL SODIUM-PENTYLENETETRAZOL COMBINATIONS AND PENTOBARBITAL SODIUM CONTROLS. As indicated in Table 1, ten volunteers received orally from 1,300 to 2,000 mg. of pentobarbital sodium together with 3,900 to 6,000 mg. of pentylenetetrazol. All subjects exhibited some signs of mild acute barbiturate intoxication, strongly resembling those of acute alcoholism. They either remained awake until their usual bedtime or were easily aroused if they fell asleep. In the latter case, they were able to respond to questions, sometimes without effort, other times slowly and in a dysarthric manner. They all showed ataxia in gait and station, nystagmus both horizontal and vertical, and difficulty in accommodation. In some subjects there was a positive Babinski. Superficial and deep tendon reflexes, blood pressure, pulse and respiratory rates in all subjects were not significantly changed.

Evidence of central nervous system stimulation was observed in most, but not in all, subjects. Seven out of 10 subjects showed nausea, retching and vomiting within 1 to 4 hours after ingestion. Frank convulsions were never seen, but in 4 subjects involuntary clonic jerks and infrequent torsion spasms were observed. It is worthy of note that these signs were not seen in the subjects who ingested the largest amounts of pentylenetetrazol.

The results of the control group receiving pentobarbital alone are shown in Table 2. Of 6 volunteers, 3 received 800, and 3 received 1,000 mg. of pentobarbital sodium. One subject of the 800-mg. group showed first-plane anesthesia within 30 minutes, one showed deep central nervous system depression, and the third only marked dysarthria and ataxia. All those receiving 1,000 mg. of pentobarbital sodium showed marked central depression to the point of anesthesia. One volunteer exhibited, even 6 hours after administration, "light surgical anesthesia," with heavy secretions requiring frequent aspiration. Eventually all these subjects made an uneventful recovery.

When the results of the group receiving the pentylenetetrazol-pentobarbital combination are compared with the controls, the control group shows a more rapid absorption of pentobarbital. With two exceptions, maximum blood pentobarbital levels appeared in 30 minutes following oral ingestion. On the other hand, in the group ingesting the combinations, the maximum blood pentobarbital levels were reached only after 2 hours.

Marked depression or first-plane anesthesia was noted in those individuals in the control group where the pentobarbital blood level was greater than 12 mg. per liter. In the group receiving the combinations, none of these subjects was markedly depressed, although the pentobarbital levels were greater than 12 mg. per liter in 5 subjects.

The rate of disappearance of pentobarbital from the blood was the same

TABLE 1.—EFFECT OF ORAL ADMINISTRATION OF PENTOBARBITAL SODIUM AND PENTYLENETETRAZOL COMBINATIONS IN 10 HUMAN VOLUNTEERS

Case No.	*Wt. (kg.)*	*Total dose* Pentobarbital (mg.)*	*Blood Barbiturate Levels (mg./L.)*									*Comment***
			½ hr.	*1 hr.*	*2 hrs.*	*3½ hrs.*	*4½ hrs.*	*6 hrs.*	*12 hrs.*	*24 hrs.*	*36 hrs.*	
1	68	1300	0.0	2.0	5.0	5.5		5.5	4.0	3.5		Sleepy but well oriented.
2	91	1300	0.0	4.5	9.0	11.5		9.0	11.5	8.5	6.0	Retired at usual hour. Rational and alert but slightly dysarthric, somewhat ataxic.
3	64	1600	3.5	7.0	10.5	12.5		13.0	11.5	8.5	6.0	Sleepy but easily aroused.
4	65	1600	0.0	1.0	10.0	13.5		13.5	11.6	10.0	6.5	Slight clonic jerks; fell asleep 6 hrs. after given drug.
5	69	1600	1.8	5.5	7.5	8.0		7.5	6.5	5.5	3.0	Same as Case 4.
6	65	1700	3.5	7.0	9.0	9.0		9.0				Not somnolent until late at night; slight ataxia.
7	75	1800	4.0	10.0	17.0	18.0		17.5	14.0	12.5	12.0	Torsion spasm and occasional clonic jerks but rational.
8	73	1800	1.3	7.5	11.0	11.8		17.0	14.1	10.8	10.3	Dysarthric and ataxic; fell asleep after 6 hrs. Infrequent torsion spasms.
9	77	2000	0.0	1.5	5.5	9.2	9.5	9.0	8.5		5.5	Fell asleep 3½ hrs. after given drug; easily aroused and then rational.
10	92	2000	0.0	1.5	12.5	15.5	14.0	13.0	12.0		8.0	

* The total dose of pentylenetetrazol in each case was 3 times that of the barbiturate. It varied, therefore, from 3.9 gm. to 6.0 gm.

** Patients 1, 3, 4, 5, 6, 9 and 10 vomited from 45 minutes to 3¾ hours following administration of the drug.

in both groups (approximately 1.5% per hour), indicating that pentylenetetrazol had no effect on the removal of pentobarbital from the blood. (Fig. 1.)

B. SECOBARBITAL SODIUM-PENTYLENETETRAZOL COMBINATIONS. The results presented in Table 3 showed that none of these subjects exhibited signs of marked barbiturate depression. The only barbiturate effects were as follows: light sleep from which they could be easily aroused, dysarthria and motor incoordination. Only two of the subjects showed muscle twitches which may be attributed to pentylenetetrazol. One of these subjects became excited and was subsequently sedated with 200 mg. sodium amobarbital intravenously. Four of the 6 subjects vomited from 35 minutes to 4½ hours following ingestion. An examination of the vomitus of 2 subjects revealed appreciable amounts of the barbiturate.

The concentration of secobarbital in the blood varied considerably. Maximum absorption of the drug, as judged by blood levels, appeared to take place after 2 hours, with the exception of subject C.W., who reached the high level of 13.8 mg. per liter within one hour and maintained a high level for over 6 hours. During this time he showed only mild effects of barbiturate intoxication. Three of the 6 subjects reached high levels of over 9 mg. per liter. The rate of fall of the secobarbital blood level was approximately 2.5% per

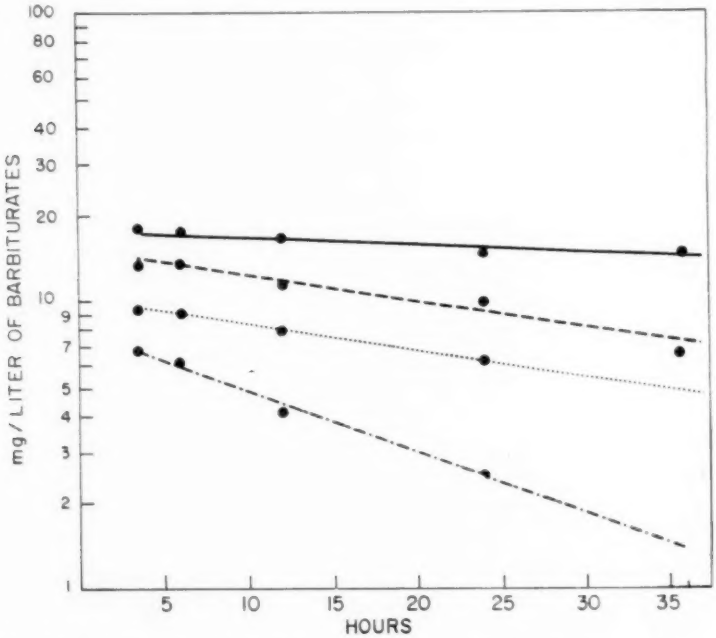

Fig. 1.—The Rate of Disappearance of Barbiturates from the Blood. Ordinate: milligrams per liter of barbiturates. Abscissa: time (hours). Uppermost line: phenobarbital administered in connection with pentylenetetrazol. Second line: pentobarbital sodium administered with pentylenetetrazol. Third line: pentobarbital sodium. Fourth line: secobarbital sodium administered with pentylenetetrazol.

TABLE 2.—EFFECT OF ORAL ADMINISTRATION OF PENTOBARBITAL SODIUM IN 6 HUMAN VOLUNTEERS

Case No.	Wt. (kg.)	Total dose Pentobarbital (mg.)	Blood Barbiturate Levels (mg./L.) ½ hr.	1 hr.	2 hrs.	3½ hrs.	6 hrs.	12 hrs.	24 hrs.	Comment
1	94	800		1.0	5.0	6.5	5.0	4.0	3.5	Marked dysarthria and ataxia.
2	63	800		3.5	11.8	10.8	9.5	8.8	6.0	Not easily awakened; responded only to deep pain. Later showed first plane anesthesia.
3	63	800	12.0	10.2	9.7	8.9	8.3	7.3	5.0	Same as Case 1.
4	73	1000	15.0	12.0	10.0	9.5	9.5	8.0	6.5	First plane anesthesia 42 min. after drug. Recovery from anesthesia after 12 hrs.
5	80	1000	12.5	10.3	9.3	8.2	8.0	7.0	5.0	Same as Cases 1 and 3, except unconscious for almost 2 hrs.
6	60	1000	16.6	15.0	13.5	12.8	12.0	10.3	8.7	Became deeply narcotized 15 min. after given drug. Showed first plane or second plane anesthesia, requiring frequent aspiration. Became lighter after 6 hrs.

hour (Fig. 1). All subjects made a complete and uneventful recovery.

C. PHENOBARBITAL SODIUM-PENTYLENETETRAZOL COMBINATIONS. The results in 6 subjects who received from 2,000 to 4,100 mg. of phenobarbital and from 3,000 to 6,150 mg. of pentylenetetrazol are presented in Table 4. All of the subjects were mildly sedated and were easily aroused; ambulation was good, and they recovered in 36 hours. The subject who received the largest dose (4.1 gm.) became dysarthric and ataxic 6 hours after administration, with a blood level of 66.5 mg. per liter; after 96 hours, he was still somewhat ataxic, dysarthric, and emotionally disturbed, with a blood level of 51 mg. per liter. Vomiting in this group usually occurred between 3 and 5 hours after administration. There was recurrence of vomiting in one subject after 7 hours.

Maximum absorption of the drug, as indicated by the blood levels, was slow and occurred generally from within 6 to 12 hours after administration. The rate of disappearance of phenobarbital from the blood was approximately 0.7% per hour (Fig. 1).

Discussion. The above findings indicate that pentylenetetrazol, in combination with barbiturates, affords protection against the central depressant effects of the latter. There are several mechanisms by which pentylenetetrazol may exert its protective effect: 1) physiological antagonism, 2) inducing vomiting, and 3) delaying absorption.

1. PHYSIOLOGICAL ANTAGONISM. The mechanism by which pentylenetetrazol and other central stimulants antagonize the effects of barbiturates is not understood. Torda[17] believes that pentylenetetrazol induces central stimulation by increasing the acetylcholine content of the brain along with another unknown process. Clinical and laboratory observations demonstrate that acute intoxication with either barbitu-

TABLE 3.—EFFECT OF ORAL ADMINISTRATION OF SECOBARBITAL SODIUM AND PENTYLENETETRAZOL COMBINATIONS IN 6 HUMAN VOLUNTEERS

Case No.	*Wt. (kg.)*	*Total dose* Secobarbital Sodium (mg.)*	*Blood Barbiturate Levels (mg./L.)*								*Comment***
			½ hr.	*1 hr.*	*2 hrs.*	*3½ hrs.*	*4½ hrs.*	*6 hrs.*	*12 hrs.*	*24 hrs.*	*48 hrs.*	
1	79	1300		13.8	13.3	13.3		11.0	8.0	5.3	3.3	Dysarthric and ataxic; finally fell asleep. Answered questions in dysarthric fashion, 6 hrs. later.
2	68	1300		7.0	8.3	7.0		6.5	4.2	2.5	0.0	Dysarthric but well oriented. Twitches about face when awake, but disappeared when asleep.
3	76	1500	2.5	4.0	5.0	4.5		4.0	3.0	2.5	1.0	Awake and well oriented.
4	68	1500	1.0	4.0	7.0	7.5		9.5	12.0	10.5	4.0	Olfactory hallucinations and nystagmus; dysarthric and ataxic. Slight disorientation, muscle twitches and combativeness, 6 hours later. Fell asleep 11 hrs. after drug was given.
5	93	1500	0.0	2.0	2.5	7.0		9.5	8.0	7.0	2.5	Completely rational and only very slightly dysarthric. Fell asleep 12 hrs. after drug was given.
6	75	1500	0.0	0.0	0.0	2.0	5.8	5.6	5.4	4.5	1.0	Dysarthric and sleepy, well oriented and cooperative. Asleep at usual bedtime.

* The total dose of pentylenetetrazol in each case was 3 times that of the barbiturate. It varied, therefore, from 3.9 gm. to 4.5 gm.

** Cases 1, 2, 3 and 6 vomited from 35 min. to 4½ hrs. after drug was given. In Case 1, 66.5 mg. of secobarbital was recovered from vomitus; in Case 2, 250 mg.; in Case 3, 784 mg. The vomitus of Case 6 was not analyzed.

TABLE 4.—EFFECT OF ORAL ADMINISTRATION OF PHENOBARBITAL SODIUM AND PENTYLENETETRAZOL COMBINATIONS IN 6 HUMAN VOLUNTEERS

Case No.	*Wt. (kg.)*	*Total dose* Phenobarbital Sodium (mg.)*	*Blood Barbiturate Levels (mg./L.)*									*Comment***
			1 hr.	*3 hrs.*	*6 hrs.*	*12 hrs.*	*24 hrs.*	*36 hrs.*	*48 hrs.*	*72 hrs.*	*96 hrs.*	*120 hrs.*	
1	80	2000	0.0	23.0	36.0	36.0	33.0	32.0	31.0	28.0			Asleep at usual bedtime; easily aroused and completely rational.
2	82	2000	0.0	28.0	29.0	31.0	31.0	29.0	29.0	25.0			Same as Case 1.
3	84	3000	0.0	6.0	16.0	48.0	44.0	39.0	35.0				Alert and well oriented 7 hrs. after being given drug combination. Slept quietly but easily aroused 12 hrs. later. Next day well oriented but lethargic.
4	78	3000	2.0	11.0	14.0	12.5	11.0	10.0	9.5				No ataxia or dysarthria. Sleepy but unable to fall asleep. Slept restfully in evening.
5	80	4000	4.5	18.0	17.5	16.4	14.5		14.0	9.5			Fell asleep 5 hrs. after drug was given; easily aroused and completely rational. Gait, normal. Went to sleep at midnight, easily aroused; but his gait was unsteady.
6	77	4100	10.0	20.0	50.0	66.5	66.5		65.0	60.0	51.0	41.0	Fell asleep 5½ hrs. after drug was given; easily aroused. Slightly ataxic and dysarthric. Showed staggering gait and slurred speech 24 hrs. later. Slightly ataxic and dysarthric 96 hrs. later. From 36 to 96 hrs. after drug was given, he was emotionally upset.

* The total dose of pentylenetetrazol in each case was 1½ times that of the barbiturate. It varied, therefore, from 3.0 to 6.15 gm.

** Cases 1, 4 and 5 vomited from 3 hrs. to 7 hrs. following administration of the drug.

rates or pentylenetetrazol can be effectively treated by parenteral administration of the antagonistic drug. The results of the present study show that this antagonism prevents or minimizes the severe toxic effects of each drug even when administered orally together in fixed mixtures to human subjects. Many of our subjects received about twice the average convulsive dose of pentylenetetrazol without showing convulsions[1,7] and, as will be pointed out later, the doses of barbiturates administered to the same subjects were in the comatose and possibly fatal range. The only overt evidences of pentylenetetrazol effect in the subjects who received large doses of pentylenetetrazol with pentobarbital sodium and pentylenetetrazol with secobarbital sodium (ratio 3:1) were occasional torsion spasms and clonic jerks. On the other hand, subjects receiving pentylenetetrazol and phenobarbital combinations (ratio 1.5:1) never had torsion spasms or clonic jerks, although the amount of pentylenetetrazol administered was of the same order of magnitude as that given some of the subjects along with pentobarbital. This would suggest that in humans phenobarbital is more completely antagonistic to the central stimulating effects of pentylenetetrazol.

The depth of barbiturate depression was not as great when pentylenetetrazol was administered simultaneously with barbiturates in fixed ratios. In fact, the majority of subjects who received pentobarbital alone in doses of about half that given simultaneously with pentylenetetrazol became anesthetized, while the subjects receiving the combinations were never anesthetized and in some instances showed only ataxia and dysarthria.

2. INDUCTION OF VOMITING. Pentylenetetrazol stimulates the vomiting center when administered in average convulsive doses (total dose 3.0 to 3.6 gm.)[7]. Even in the presence of large doses of barbiturates (see tables) pentylenetetrazol can still excite the vomiting mechanism. This was least apparent in the group receiving phenobarbital-pentylenetetrazol combinations. The induction of vomiting could obviously be an important factor in the prevention of severe barbiturate poisoning. As the tables indicate, when the vomitus was analyzed for its barbiturate content, appreciable amounts were recovered. The above observations furnish evidence that phenobarbital continues to be absorbed up to 12 hours and suggest that careful gastrointestinal lavage with alkaline Ringer's solution may be a life-saving measure in such cases.

The emetic effect of pentylenetetrazol in severely barbiturized subjects is not surprising in view of the study of Schwartz[15] which showed that pentylenetetrazol is capable of denarcotizing the emetic mechanism depressed by barbiturates. The induction of vomiting is another example of physiological antagonism, since it is inconceivable that a centrally-acting drug would be capable of inducing emesis without lifting the barbiturate depression of the central vomiting mechanism.

In this connection it should be emphasized that large doses of orally administered pentylenetetrazol are not short-acting, because it may induce vomiting even as long as 7 hours following the administration of the combinations.

In view of the fact that the pentylenetetrazol-phenobarbital combinations produced neither torsion spasms nor clonic jerks and that phenobarbital is the longest acting of the barbiturates studied, it may be worthwhile to increase the ratio of pentylenetetrazol in the pentylenetetrazol-phenobarbital combinations.

3. DELAYED ABSORPTION. Tables 1 and 2 show that there is a significantly more

rapid absorption of pentobarbital sodium alone than of pentylenetetrazol-pentobarbital sodium mixtures. The delayed absorption is apparently due to the presence of pentylenetetrazol in the combinations.

A possible explanation of the effect of pentylenetetrazol on intestinal absorption of barbiturates may be found in the data reported by Van Liere and Northrup[18]. They showed that sodium amytal caused an average decrease of the emptying time of the stomach of about 20%. If pentylenetetrazol antagonized this effect of barbiturates, it would account for the slower intestinal absorption of the latter compounds. If pentylenetetrazol should delay the absorption of all barbiturates, gastric lavage would be particularly indicated in patients ingesting massive doses of mixtures of pentylenetetrazol and barbiturates.

Our own observations, as well as data in the literature, indicate that doses of both pentylenetetrazol and barbiturates ingested by our volunteers were in the convulsant or coma-producing range. Coma following oral ingestion of pentobarbital sodium has been reported to result from approximately 1 gm.[10,16]. Fisher and co-workers[3] have reported patients who have taken 0.8 and 2 gm. of pentobarbital to be in coma. Our own control studies demonstrate that 1 gm. of pentobarbital is capable of producing severe depression. On the other hand, 2 gm. of pentobarbital when given in combination with pentylenetetrazol were tolerated without severe depression. Secobarbital appears to be acutely more toxic than pentobarbital. A review of the literature[8] disclosed that only 2 of 11 cases ingested more than 2 gm. of secobarbital. In 2 cases coma followed the ingestion of as little as 0.8 gm. One patient who ingested 2 gm. succumbed after 39 hours. None of our volunteers, even though ingesting from 1.3 to 1.5 gm. of secobarbital in combination with pentylenetetrazol, was even lightly narcotized.

The acute toxic dose of phenobarbital is larger than that of either pentobarbital or secobarbital. Coma has been reported to occur[8] from doses ranging from 1.5 to 4.8 gm., while death occurred from doses ranging from 4 to 5.2 gm. In the present study as much as 4.1 gm. of phenobarbital when combined with 6.15 gm. of pentylenetetrazol failed to anesthetize the subject.

Pohlisch and Panse[14] reported that the minimal fatal dose of phenobarbital is about 2.4 gm., while the median fatal dose is about 6 gm. It appears that death can occur with relatively low doses (2 to 4 gm.) when no treatment is given. Leschke[11] reported that in the city hospitals of Budapest between 1925 and 1928 there were 131 cases of phenobarbital poisoning with 10 fatalities. The average fatal dose was 4 gm.

Blood barbiturate levels are probably the most reliable indication of the degree of central nervous system depression of poisoned patients. A review of the pertinent literature discloses that many of the blood levels noted in this report, after ingestion of mixtures of barbiturates and pentylenetetrazol, are in the toxic and, possibly, even in the lethal range. Fisher *et al.*[3] reported comatose cases of pentobarbital poisoning with blood levels ranging from 10 to 16 mg. per liter. According to Fisher and Freimuth[4], pentobarbital and secobarbital cause coma when the blood level rises to 10.0 to 20.0 mg. per liter. In a further series of cases they found that phenobarbital caused coma with blood levels of 70 mg. per liter. Recovery was seen occasionally with blood levels of 51.0 mg. per liter of pento-

barbital and 128 mg. per liter of phenobarbital.

Lous[12] found that most patients with severe or moderately severe acute phenobarbital poisoning can be awakened when the blood levels fall to 50.0 to 100 mg. per liter of blood, but their consciousness is still impaired. The same author[13] reported, however, that the oral administration of 750 mg. of phenobarbital resulted in a blood level of approximately 30 mg. per liter, while our subjects who received more than five times that amount of phenobarbital in combination with metrazol, had a blood level of a little less than 70 mg. per liter. For this discrepancy, we have no explanation. Gradwohl[6] reported that 70 mg. per liter of phenobarbital may cause coma. The above data are in accord with the blood barbiturate concentration of patients admitted to hospitals with which the authors are connected.

If we compare the doses and blood levels reported in the literature on barbiturates with the data in this paper, obtained following the ingestion of the combinations of pentylenetetrazol and barbiturates, it is apparent that the pentylenetetrazol had a considerable protective action in the volunteers who took large doses of barbiturates.

It should be added that the above described combinations are fixed mixtures. As Koppanyi and Lieberson[9] have pointed out, fixed mixtures are not always rational and in most cases should be condemned because of the unequal elimination of the components of the mixtures. This objection to fixed mixtures, however, applies only to pharmacotherapeutics because individual drugs comprising the mixture can be given separately and according to the requirements of the patient. Such a procedure is obviously impossible when one deals with a drug mixture designed for protection. To prevent suicide and unintentional overdosing with barbiturates, the barbiturate and analeptic must be combined in one capsule or tablet. The person contemplating suicide, or the amnesic individual, obviously will not take pentylenetetrazol if prescribed separately because in the one instance it would defeat his purpose, and in the other, he would be unable to remember to do so. It is, therefore, necessary that if a protective drug is used with barbiturates, it must be combined in a fixed mixture even if the elimination of both drugs does not occur at exactly the same rate. As a matter of fact, Koppanyi and Fazekas have shown that oral administration of pentylenetetrazol in large doses is fairly long-acting and that some of the pentylenetetrazol effects may last for as long as 24 hours. It is interesting to observe in this connection that it was reported[2] that in mice the pentylenetetrazol effects may outlast those of pentobarbital sodium.

Summary. 1. The ingestion of from 1,300 to 2,000 mg. of pentobarbital sodium simultaneously with three times the amount of pentylenetetrazol produced no anesthesia nor severe central depression in human volunteers. The ingestion of from 800 to 1,000 mg. of pentobarbital sodium alone, however, resulted in most cases in marked central nervous system depression and, in the majority of cases, in light surgical anesthesia.

2. Pentobarbital sodium was absorbed more rapidly from the gastrointestinal tract than fixed mixtures of pentobarbital sodium and pentylenetetrazol.

3. The rate of disappearance of pentobarbital from the blood is the same in both groups, approximately 1.5% of the ingested dose per hour.

4. Subjects ingesting secobarbital sodium in doses from 1,300 to 1,500 mg.

with three times the amount of pentylenetetrazol showed no signs of marked barbiturate depression. The rate of fall of the blood levels was approximately 2.5% per hour.

5. Subjects ingesting phenobarbital sodium in doses from 2,000 to 4,100 mg. with one and one-half times as much pentylenetetrazol were only sedated and could easily be aroused. The rate of disappearance of this barbiturate from the blood was approximately 0.7% per hour.

6. Many subjects who took the barbiturate-pentylenetetrazol combinations vomited, indicating denarcotization of the vomiting mechanism.

7. The control experiments, as well as the review of the pertinent literature, indicate that pentylenetetrazol is an efficient preventative when taken simultaneously with comatose or possibly fatal doses of barbiturates.

8. Pentylenetetrazol given in these combinations and in the above stated dose ranges did not produce convulsions. Therefore, in the human, under the above conditions, pentylenetetrazol and barbiturates are mutually antagonistic.

ACKNOWLEDGMENT. We wish to acknowledge the technical assistance of Mr. Leo Kazyak, working under the direction of one of us (Dr. Goldbaum), in performing the blood barbiturate analysis.

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(Interlingua on page 600)

THE RESPONSE TO RESCINNAMINE ADMINISTERED PARENTERALLY AND ORALLY FOR THE TREATMENT OF HYPERTENSION*

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Following the introduction of *Rauwolfia serpentina*[7] for the treatment of hypertension, favorable clinical reports have stimulated extensive investigation of this crude drug, alkaloidal extracts of the drug, as well as numerous single alkaloids which have since been isolated. Reserpine was the first effective anti-hypertensive alkaloid[2-4,8] of the group to be so isolated[6]. Originally it was thought that reserpine was the only alkaloid with any hypotensive activity[8], but since the known compounds accounted for less than 50% of the activity of alseroxylon†[1], it seemed logical to look for additional active principles in the amorphous portion of this preparation. Klohs and his co-workers[5] succeeded in extracting and identifying chemically the trimethoxycinnamic ester of methyl reserpate which has been designated rescinnamine. The following report presents an evaluation of this alkaloid when used for the treatment of mild to moderately severe hypertension. The study has been divided into two parts: 1) patients who received the drug parenterally and 2) patients who were given the drug orally for 2 to 4 months or more as outpatient treatment of their hypertension.

Methods. PART I. PARENTERAL ADMINISTRATION OF RESCINNAMINE. Twenty-six unselected hypertensive patients were given rescinnamine parenterally in doses ranging from 2.5 to 15 mg. The patients were observed for from 6 to 24 hours after injection of the drug and supine and upright blood pressures were recorded every 30 minutes during this period. During the initial studies, some patients received graded doses of the drug, at least one week apart, in order to establish the most effective dose as well as the dose at which side effects were not prohibitive. From these initial studies, it was ascertained that the optimal dose was 10 mg. Subsequently, 20 patients who were given this dose were studied in detail for blood pressure response and side effects. In addition, 8 of the 20 patients also received separate injections of reserpine at least one week apart to compare the effect of the two alkaloids in the same patients.

PART II. ORAL ADMINISTRATION OF RESCINNAMINE. A group of 84 unselected ambulatory hypertensive patients with mild to severe hypertension were treated with oral rescinnamine for 2 months (Period D_1); 64 of these were treated for an additional 2 months or more (Period D_2). During a control period, all patients received a complete initial workup including an electrocardiogram, chest roentgenogram, and blood urea nitrogen determination. These were repeated at regular

*Supported in part by a grant from the Houston Heart Association.

†Available as Rauwiloid from Riker Laboratories, Inc.

intervals. Each patient was started on placebo tablets for a period of one month as a control. During this time he was seen weekly. Side effects, physical findings (including upright and supine blood pressure and pulse rates) and alteration in symptoms due to their disease were recorded at each visit.

At the end of the placebo control period, all but 10 of the 84 patients were started on oral rescinnamine, 2.0 mg. daily, in divided doses of 0.5 mg. four times daily. The 10 exceptions received 4.0 mg. daily to compare the effectiveness of this larger dose with the 2.0 mg. dose. Such doses were continued for 2 months (Period D_1) and, during this time, weekly recordings of supine and upright blood pressure plus review of symptoms were made. Following the initial 2-month period of observation, 64 of the 84 patients were continued on rescinnamine for an additional 2 months or more (Period D_2) receiving either 2 or 4 mg. per day. The group receiving 4 mg. per day consisted of 31 patients who had not become normotensive while receiving 2.0 mg. per day during Period D_1. Thirty-three patients were continued on the same 2 mg. dose during the second drug period (D_2) that they received during Period D_1. Twenty of the 84 patients who were observed during Period D_1 were not followed during Period D_2. Ten of these 20 patients were dropped from the study after Period D_1 because of progression of their disease or complications which necessitated more active antihypertensive therapy. The remaining 10 patients who were dropped during the second drug period were those who initially started on the larger 4-mg. dose. At the completion of the study, a complete review of physical findings and pertinent laboratory data were again recorded.

Results. PARENTERAL THERAPY. Twenty-six unselected hypertensive patients received parenteral rescinnamine. These were patients whose control pressures had been established during the month they were receiving placebos. Each patient received parenteral injections of rescinnamine followed by supine and upright blood pressure determinations every 30 minutes for the ensuing 6 to 24 hours. In patients who participated in two or more tests, the test periods were separated by 1 or 2 weeks during which time placebos were given. Several patients received the drug intravenously in 200 ml. of dextrose in water and the remaining patients received the drug by intramuscular injection. No difference in response between the two routes of administration was observed.

In order to establish the optimal therapeutic dose, increasing doses of the drug varying from 2.5 to 15 mg. were given. Five patients received 2.5 mg., 5 mg. and 10 mg. Only one of the patients receiving 2.5 mg. showed a reduction in mean blood pressure in excess of 20 mm. Hg and this was seen only in the upright position. Of the 5 patients who received 5 mg., 3 showed a reduction in mean upight blood pressure in excess of 20 mm. Hg, this occurring in only one patient in the supine position. A total of 20 patients were given 10 mg. because initial observations indicated that this 10-mg. dose of rescinnamine was a very effective and well tolerated dose whereas 15 mg. produced excessive side actions consisting of weakness, dizziness, nasal congestion and tendency to syncope. Therefore, only 3 patients were given this large 15 mg. dose. Of the 20 patients who received a dose of 10 mg. of rescinnamine, 18 (90%) demonstrated a significant reduction* in blood pressure (Table 1). Fourteen patients became normotensive†, 7 of whom had control diastolic pressures above 120 mm. Hg. The most marked blood pressure reduction usually occurred during the 5th to 6th hours ($p<0.001$) after parenteral administration (Figs. 1 and 2) and at this time, a tendency to postural hypotension was noted (Fig. 1).

*A reduction of 20 mm. Hg in mean blood pressure was considered a significant response.

†Reduction in blood pressure to below 150 systolic and 100 diastolic.

TABLE 1.—RESPONSE TO PARENTERAL RESCINNAMINE

	Control					*One Hour*					*Two Hours*					*Three Hours*			
	Upright		*Supine*			*Upright*		*Supine*			*Upright*		*Supine*			*Upright*		*Supine*	
Patients	*S*	*D*	*S*	*D*		*S*	*D*	*S*	*D*		*S*	*D*	*S*	*D*		*S*	*D*	*S*	*D*
1 D.W.	197	119	218	127		186	110	178	110		154	112	158	106		150	102	174	106
2 J.W.	185	132	217	140		150	110	190	125		170	130	190	130		150	120	200	130
3 H.L.	200	123	207	113		180	120	170	110		190	110	180	110		160	100	170	90
4 L.J.	172	114	166	106		160	104	146	100		156	110	148	104		130	100	160	110
5 A.S.	169	106	186	103		150	90	174	108		144	84	170	94		140	84	184	90
6 B.D.	190	120	190	121		166	130	174	112		156	110	164	114		126	84	126	80
7 J.G.	243	133	265	132		222	128	220	130		190	110	200	120		130	80	210	120
8 C.M.	187	131	197	131		172	112	192	124		156	102	184	110		128	72	146	90
9 P.W.	194	106	207	118		182	98	198	118		182	98	184	106		170	92	178	106
10 E.H.	199	131	209	130		160	110	176	114		180	120	180	120		152	110	164	112
11 E.R.	220	148	203	132		196	130	194	130		170	110	180	110		140	100	180	105
12 B.B.	181	106	189	97		164	106	180	98		170	108	178	100		170	110	190	106
13 T.McC.	195	132	199	125		210	136	198	124		205	120	190	105		198	124	184	120
14 J.S.	181	116	175	115		150	116	170	110		122	112	164	118		134	110	152	116
15 J.B.D.	197	125	229	130		192	128	214	122		166	116	198	118		206	120	218	124
16 J.G.	259	128	257	121		214	120	234	116		230	128	224	110		246	106	234	110
17 J.B.	199	123	200	125		216	120	208	106		200	130	210	116		184	120	186	98
18 M.Y.	215	113	226	109		206	102	196	84		220	100	206	94		176	82	198	100
19 R.J.	226	136	226	138		194	130	214	128		200	142	214	136		200	118	214	112
20 B.T.	153	85	159	90		158	90	164	100		148	100	170	100		170	100	160	100
Mean	198	121	206	120		181‡	115‡	190‡	113‡		175‡	113‡	185‡	111‡		163‡	102‡	181‡	106
M.M.	196	110	189	105		180	100	160	100		150	95	165	90		150	82	160	80
M.B.	202	113	233	114		198	100	200	100		196	100	219	110		185	100	190	100
E. B.	271	131	284	123		220	120	230	110		200	110	220	110		188	98	188	104
Mean	223	118	235	114		199	107	197	103		182	102	201	103		174	93	179	95

Rescinnamine Administered

Key to table: S = Systolic Pressure D = Diastolic Pressure

‡ = $P<0.01$; $t = x\sqrt{\frac{n(n-1)}{Sx^2}}$

Of the side effects recorded after the administration of 10 mg. of rescinnamine (optimal dose) dizziness was the most common complaint, occurring in 15 of the 20 patients. Thirteen complained of being sleepy. Nine complained of weakness. Nine also were observed to have nasal congestion and conjunctival injection. Five patients complained of headache at the time of maximum blood pressure reduction. One patient developed frank urticaria with marked postural hypotension which was readily alleviated by an oral antihistamine. Other less frequent complaints noted were chilly sensations, heaviness of head, blurred vision, and trembling. One patient noted prolonged and severe pain at the site of drug injection. The majority of the patients demonstrated a bradycrotic effect after rescinnamine. This effect was considered significant only when the pulse rate was reduced 10 beats or more per minute. The average reduction for the entire parenteral group was only 6 beats per minute.

Table 2 compares the effect of parenteral rescinnamine in 8 hypertensive patients who also received parenteral reserpine at least one week later. By previous titration studies, it had been observed that approximately 10 mg. of rescinnamine were equivalent to 5 mg. of reserpine when given parenterally. These respective doses were, therefore, used in each of the 8 patients who were given the 2 drugs at appropriately spaced intervals, in order to prevent an overlapping hypotensive response.

IN PATIENTS WITH HYPERTENSION

Four Hours				*Five Hours*				*Six Hours*				*Twenty-four Hours*				
Upright		*Supine*		*Upright*		*Supine*		*Upright*		*Supine*		*Upright*		*Supine*		
S	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*Total Dose mg. I.M.*
150	96	173	136	176	124	170	102	146	96	166	116	170	100	182	104	10
190	120	210	130	176	130	–	–	225	125	195	135	170	122	190	130	10
168	100	178	100	160	100	–	–	170	90	164	90	190	114	196	110	10
164	96	178	100	122	78	142	80	130	90	140	90	144	96	152	94	10
124	80	154	80	130	80	180	100	120	85	160	100	–	–	–	–	10
114	88	138	90	118	98	156	100	122	94	144	90	138	104	130	90	10
110	75	180	110	90	50	180	100	180	100	220	120	–	–	–	–	10
122	72	112	72	106	70	120	80	92	58	136	92	160	82	162	92	10
152	86	178	92	170	90	182	100	178	106	176	108	–	–	–	–	10
130	100	170	110	150	110	170	120	128	98	152	102	182	110	196	118	10
92	66	164	94	120	88	160	90	142	90	180	92	–	–	–	–	10
170	100	190	110	150	95	170	90	178	110	174	100	–	–	–	–	10
188	118	184	112	190	110	190	100	206	120	–	–	198	130	228	126	10
120	102	160	110	118	92	132	104	80	60	106	80	–	–	–	–	10
180	110	198	110	198	116	200	114	200	112	194	112	–	–	–	–	10
260	104	–	–	224	106	200	96	190	100	230	106	–	–	–	–	10
176	98	132	84	152	98	152	78	160	110	164	106	230	115	226	112	10
194	98	198	94	184	92	194	102	192	108	202	106	–	–	–	–	10
210	115	–	–	250	140	–	–	218	122	254	132	164	104	174	104	10
140	80	144	80	140	80	150	80	140	90	150	80	–	–	–	–	10
158‡	95‡	169‡	101‡	156‡	97‡	168‡	96‡	160‡	98‡	174‡	103‡					
120	80	140	90	128	84	130	90	124	80	140	80	150	90	160	88	15
170	100	200	100	200	100	200	100	200	100	210	110	180	88	180	90	15
160	90	180	100	176	96	198	90	178	100	200	90	220	90	220	90	15
150	90	173	97	168	93	176	93	167	93	183	93	183	89	187	89	

PARENTERAL RESCINNAMINE - A COMPARISON OF SUPINE AND UPRIGHT PRESSURES

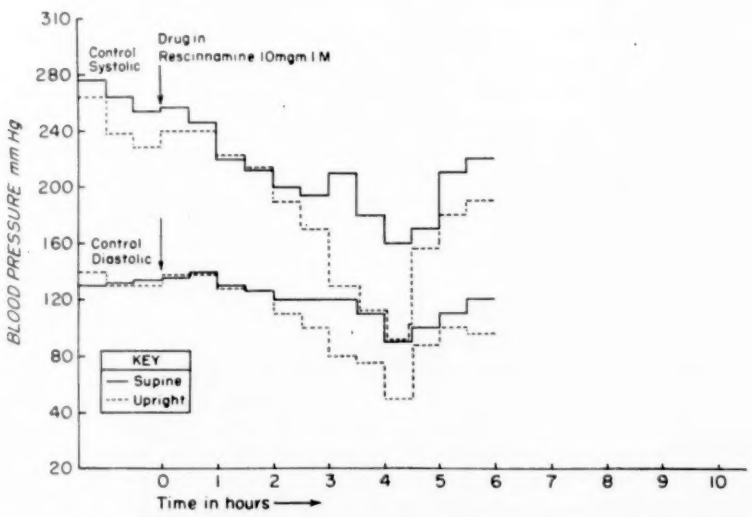

Fig. 1.—Typical supine and upright blood pressure response to parenteral rescinnamine given to a patient with hypertension.

TABLE 2.—THE BLOOD PRESSURE RESPONSE TO RESERPINE AS

		Control				*One Hour*				*Two Hours*				*Three Hours*			
		Upright		*Supine*		*Upright*		*Supine*		*Upright*		*Supine*		*Upright*		*Supine*	
Patient		*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*
1 D.W.	Reserpine Administered	162	102	185	106	112	84	156	94	118	78	170	102	110	74	146	88
2 P.W.		232	131	222	131	240	130	218	118	212	114	230	130	214	120	204	130
3 C.M.		208	132	215	128	182	112	202	112	184	110	178	120	142	94	146	90
4 J.S.		163	120	174	112	144	100	150	102	146	110	166	110	140	98	140	90
5 J.G.		213	101	196	102	174	86	176	84	160	80	150	84	122	60	160	80
6 J.B.		188	120	187	105	170	110	178	108	180	110	176	98	170	110	176	82
7 M.Y.		199	111	204	103	184	92	200	86	180	96	166	98	176	98	180	94
8 B.T.		163	100	163	93	150	100	155	100	150	100	160	90	140	80	142	80
Mean		191	115	193	110	170‡	102‡	179‡	101*	166‡	100‡	175*	104*	152‡	92‡	162‡	92‡
1 D.W.	Rescinnamine Administered	197	119	218	127	186	110	178	110	154	112	158	106	150	102	174	106
2 P.W.		194	106	207	118	182	98	198	118	182	98	184	106	170	92	178	106
3 C.M.		187	131	197	131	172	112	192	124	156	102	184	110	128	72	146	90
4 J.S.		181	116	175	115	150	116	170	110	122	112	164	118	134	110	152	116
5 J.G.		259	128	257	121	214	120	234	116	238	128	224	110	246	106	234	110
6 J.B.		199	123	200	125	216	120	208	106	200	130	210	116	184	120	186	98
7 M.Y.		215	113	226	109	206	102	196	84	220	100	206	94	176	82	198	100
8 B.T.		153	85	159	90	158	90	164	100	148	100	170	100	170	100	160	100
Mean		198	115	205	117	186	109*	193	109*	178*	110*	188	108	170*	98	179‡	103*

Key to table: S = Systolic
D = Diastolic

‡ = $p<0.01$; $t = \bar{x}\sqrt{\frac{n(n-1)}{S x^2}}$

* = $p<0.05$

Reserpine Administered Rescinnamine Administered

There was a significant blood pressure response in all 8 patients both after 10 mg. of rescinnamine and after 5 mg. of reserpine. The hypotensive effect of reserpine, in those patients tested, was some times slightly greater than that of rescinnamine and *vice versa*. Although the onset of significant hypotensive levels varied from 2 to 5 hours with both drugs, the average delay before maximum reduction in blood pressure due to reserpine was 3 to 4 hours whereas the maximum reduction in pressure after rescinnamine occurred at 5 to 6 hours (Fig. 4). More patients maintained a significant reduction in blood pressure for a longer period of time after rescinnamine than after reserpine. In most of the patients the blood pressure returned to or toward the control levels at the end of 24 hours. Aside from the difference in time of maximum blood pressure depression, after administration of the two drugs, it is felt that the over-all effect of reserpine and rescinnamine administered parenterally is essentially the same, both in degree of blood pressure reduction, pulse rate, and side effects.

RESULTS WITH RESCINNAMINE IN THE OUTPATIENT TREATMENT OF PATIENTS WITH HYPERTENSION. Eighty-four unselected hypertensive patients received oral rescinnamine as outpatients. In order to compare the effect of the drug in mild to more severe hypertension, the patients were divided into two groups: Group A, those patients with control diastolic pressures greater than 100 mm. Hg but less than 120 mm. Hg; Group B, those patients with diastolic pressure greater than 120 mm. Hg. Purely by coincidence, there were 42 patients in both groups and also by

COMPARED TO RESCINNAMINE ADMINISTERED PARENTERALLY

Four Hours				*Five Hours*				*Six Hours*					
S	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*	*mg.*	*Drug*
126	88	136	86	110	68	142	96	140	80	170	118	5.0	Serpasil
218	120	232	134	220	110	230	126	220	118	224	130	5.0	Serpasil
130	86	150	90	112	64	160	96	132	84	176	106	5.0	Serpasil
140	88	144	100	144	96	148	106	160	110	166	118	5.0	Serpasil
140	78	–	–	160	84	–	–	160	70	140	68	5.0	Serpasil
172	106	160	80	160	106	164	90	158	100	150	88	5.0	Serpasil
166	88	158	84	176	96	158	86	186	106	176	104	5.0	Serpasil
130	75	145	84	160	94	162	86	160	85	160	90	5.0	Serpasil
153‡	91‡	161*	94*	155*	90‡	166*	98*	165*	94‡	170*	103	5.0	Serpasil
150	96	173	136	176	124	170	102	146	96	166	116	10.0	Rescinnamine
152	86	178	92	170	90	182	100	178	106	176	108	10.0	Rescinnamine
122	72	112	72	106	70	120	80	92	58	136	92	10.0	Rescinnamine
120	102	160	110	118	92	132	104	80	60	106	80	10.0	Rescinnamine
260	104	–	–	224	106	200	96	190	100	230	106	10.0	Rescinnamine
176	98	132	84	152	98	152	78	160	110	164	106	10.0	Rescinnamine
194	98	198	94	184	92	194	102	192	108	202	106	10.0	Rescinnamine
140	80	144	80	140	80	150	80	140	90	150	80	10.0	Rescinnamine
164‡	92‡	157‡	95*	159‡	94*	163‡	93‡	147‡	91*	166‡	99‡	10.0	Rescinnamine

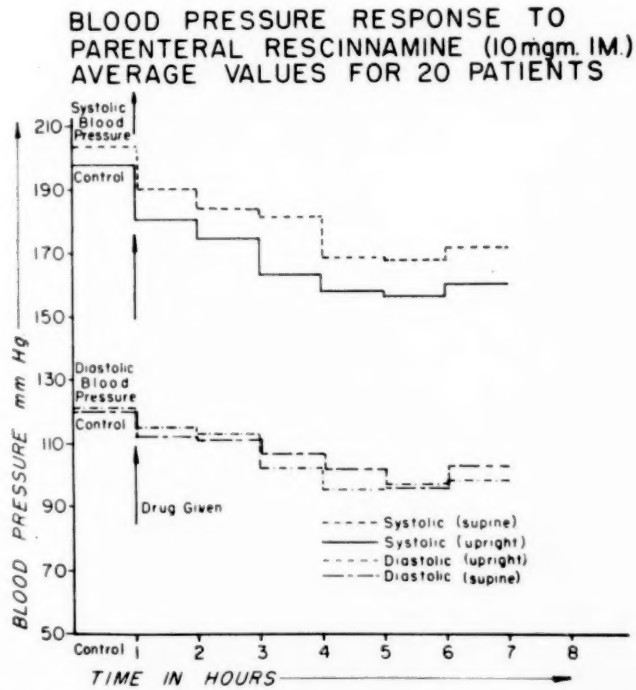

Fig. 2.—Graph of average values for 20 patients showing the upright and supine blood pressure responses to 10 mg. of rescinnamine.

BLOOD PRESSURE RESPONSE—COMPARING PARENTERAL RESERPINE WITH RESCINNAMINE

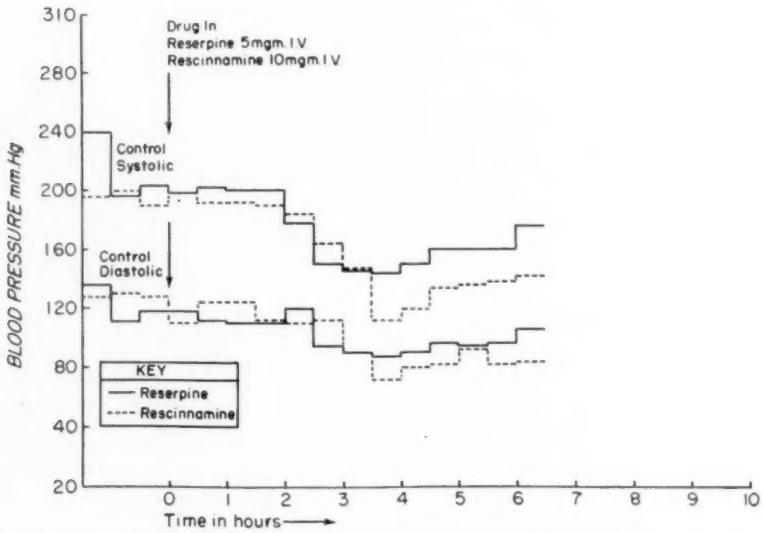

Fig. 3.—Typical blood pressure response (supine position) in a patient with hypertension who was given 5 mg. of reserpine and 10 mg. of rescinnamine parenterally on different days.

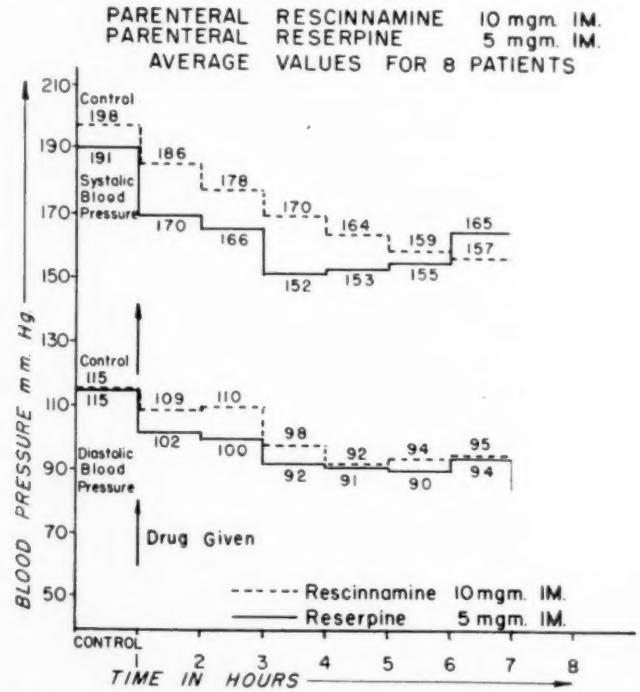

Fig. 4.—Graph of average values for 8 patients with hypertension comparing supine blood pressure response to 10 mg. of rescinnamine and 5 mg. of reserpine given parenterally.

TABLE 3.—SUMMARY OF THE CLINICAL STATUS AND COMPLICATIONS DUE TO HYPERTENSION IN PATIENTS PRIOR TO RECEIVING RESCINNAMINE THERAPY BY MOUTH

			Sex		Race		Renal Damage				Cardiac Classification‡					Cardiac Enlargement		
	Number	Average Age	M	F	W	C	0	I+	II+	III+	0	I+	II+	III+	IV+	0	Mild-Mod.	Marked
Group A*	42	53	25	17	11	31	15	10	8	9	15	11	12	3	1	9	27	6
Responsive	20	51	10	10	4	16	9	3	4	4	7	7	4	1	1	5	13	2
Unresponsive	22	54	15	7	7	15	6	7	4	5	8	4	8	2	0	4	14	4
Group B**	42	56	17	25	17	25	23	15	2	2	14	18	6	4	0	11	28	3
Responsive	19	55	9	10	10	9	12	7	0	0	9	7	3	0	0	7	12	0
Unresponsive	23	56	8	15	7	16	11	8	2	2	5	11	3	4	0	4	16	3
Total	84		42	42	28	56	38	25	10	11	29	29	18	7	1	20	55	9

	Electrocardiogram			Cerebrovascular Disease				Eye Grounds#				Angina Pectoris		
	Normal	LVH	Myocardial Damage	0	1+	2+	3+	I	II+	III+	IV+	0	1+	2+
Group A*	8	28	6	4	20	11	7	7	32	3	0	37	5	0
Responsive	3	15	2	3	10	4	3	3	16	1	0	17	3	0
Unresponsive	5	13	4	1	10	7	4	4	16	2	0	20	2	0
Group B**	12	21	9	17	15	6	4	12	29	1	0	28	13	1
Responsive	9	8	2	8	6	4	1	8	11	0	0	16	3	0
Unresponsive	3	13	7	9	9	2	3	4	18	1	0	12	10	1
Total	20	49	15	21	35	17	11	19	61	4	0	65	18	1

Key: M = Male F = Female W = White C = Negro LVH = Left ventricular hypertrophy
‡ = Classified according to American Heart Association criteria
# = Keith-Wagener-Barker Classification
* = Group A, control diastolic pressure less than 120 but more than 100 mm. Hg.
** = Group B, control diastolic pressure more than 120 mm. Hg.

coincidence, there were 42 males and 42 females distributed at random. The incidence of females was higher in the severer hypertension Group B. There were more Negro patients in both groups. Ages ranged from 26 to 70 with an average age of 55. All patients were followed (on therapy) for at least 2 months and 64 of the 84 were followed for 4 months or more.

A summary of clinical status and complications due to hypertension prior to rescinnamine therapy is presented in Table 3. Twenty-one patients (25%) had evidence of significant renal impairment; this was considered severe in 11 cases. The cardiac complications were mild and moderately severe in the majority of the patients. Eight had a functional capacity of III or IV. Only one patient complained of severe angina but 18 additional patients presented histories of precordial or substernal pain. The electrocardiograms were interpreted as being abnormal in 64 of the original 84 patients. Forty-nine showed left ventricular hypertrophy and 15 showed diffuse changes suggesting myocardial damage.

Although 35 patients complained of varying degrees of headache and dizziness, prior to therapy, only 28 (33%) of the 84 patients were considered to have significant and unquestioned cerebrovascular disease. Of these, 11 had evidence of previous cerebrovascular accidents with varying degrees of residual impairment.

Hypertensive vascular changes in the optic fundi ranged from grade I to grade III as determined by the Keith-Wagener-Barker classification. Only 4 patients in the series had changes consistent with grade III hypertensive retinopathy, while the majority of patients (73%) were classified as having grade II retinopathy. The blood pressure responses of the 84 patients receiving rescinnamine orally are presented in Table 4 (A and B). The average blood pressure values for each patient are listed before (control) and for two drug periods (D_1 and D_2) after institution of therapy, the average values being calculated at the end of 2 months (D_1) and 4 months or more (D_2). The individual determinations and the mean values for each group are listed for the responsive patients in that group, but only the mean values are listed for the unresponsive patients. A reduction in blood pressure for each patient was considered significant when the mean blood pressure (diastolic + 1/3 pulse pressure) decreased 20 mm. Hg or more after receiving the drug.*

Of the initial 84 patients treated for a period of 2 months, 40 patients (47%) showed a significant reduction in blood pressure. Of the 64 patients who continued therapy for 4 months or more, 33 (52%) showed a significant response during either period D_1 or D_2. This would indicate that with more prolonged treatment, a significant increase in blood pressure response for the group was not seen. There were 10 patients (12%) rendered normotensive (150/100 mm. Hg or less) in the group followed for 2 months, and 9 (14%) became normotensive in the group treated for 4 months. This would also indicate that the maximum effect of the drug is usually attained during the first 8 weeks of therapy. A significant and encouraging fact is that patients with diastolic pressures above 120 mm. Hg (50%) responded equally as well as those with less severe diastolic hypertension, that is, between 100 and 120 mm. Hg (45%). Except for 3 patients, however, a reduction of blood pressure to normotensive levels was obtained

*In either the supine or upright position.

TABLE 4A.—BLOOD PRESSURE RESPONSE TO RESCINNAMINE IN 42 PATIENTS WITH CONTROL DIASTOLIC PRESSURES LESS THAN 120 BUT MORE THAN 100 mm. Hg

Patients Group A	Supine Blood Pressure									Upright Blood Pressure									Pulse Rate						Dose Rescinnamine mg./24 hours	
	Control			Treatment Period D_1‡			Treatment Period D_2*			Control			Treatment Period D_1‡			Treatment Period D_2*			Supine			Upright				
	S	D	M	S	D	M	S	D	M	S	D	M	S	D	M	C	D	M	C	D_1‡	D_2*	C	D_1‡	D_2*	D_1‡	D_2*
																			Diastolic <120							
1 R.G.	162	107	125	146	93	111	131	82	98	158	112	127	144	89	107	129	78	95	96	75	72	95	77	81	2.0	2.0
2 R.A.	182	115	137	159	98	118	150	99	116	183	116	138	163	113	130	151	101	118	78	67	77	84	75	80	2.0	4.0
3 LaV.T.	225	121	156	203	102	136	181	96	124	210	117	148	180	100	127	154	89	111	72	63	73	81	62	75	2.0	4.0
4 E.W.	202	109	140	174	94	121	–	–	–	208	112	144	165	98	120	–	–	–	59	64	–	59	61	–	2.0	–
5 G.O.R.	169	92	118	151	92	112	–	–	–	195	108	137	154	99	117	–	–	–	85	84	–	93	92	–	2.0	–
6 B.D.	223	133	163	200	103	135	197	105	136	218	119	152	175	102	126	178	91	120	74	70	73	80	75	75	2.0	4.0
7 C.B.	198	99	132	165	75	105	–	–	–	191	102	132	158	87	111	–	–	–	80	75	–	84	78	–	4.0	–
8 E.C.	169	94	119	148	76	100	176	84	115	179	100	126	159	87	111	182	100	127	82	71	76	85	84	79	2.0	2.0
9 F.M.	193	109	137	165	95	118	–	–	–	188	118	141	150	100	117	–	–	–	71	72	–	84	70	–	4.0	
10 G.H.	183	107	132	182	101	128	164	98	120	167	105	126	154	93	113	137	92	107	71	61	54	77	67	63	2.0	4.0
11 R.C.	187	114	138	170	98	122	177	110	132	203	119	147	183	85	118	170	103	125	92	78	–	104	91	–	2.0	4.0
12 T.B.	193	97	129	175	94	121	166	83	111	193	104	134	172	101	125	155	82	106	74	71	72	73	75	83	2.0	4.0
13 J.L.	212	110	144	190	110	137	200	106	137	210	116	147	180	104	129	160	100	120	88	76	76	88	76	76	2.0	2.0
14 M.S.	155	100	118	150	100	117	154	102	119	155	110	125	128	98	108	150	100	117	78	64	64	80	66	70	2.0	2.0
15 C.Y.	178	102	127	150	90	110	160	90	113	184	100	128	160	98	119	149	85	106	80	60	60	82	72	60	2.0	2.0
16 P.O'D.	160	100	120	150	96	114	154	102	119	170	115	133	140	92	108	156	104	121	80	72	68	84	78	70	2.0	2.0
17 V.N.	170	100	123	134	92	106	136	84	101	180	110	133	138	96	110	134	80	98	100	60	64	98	64	66	2.0	2.0
18 R.B.	189	110	136	150	99	116	147	95	112	180	104	129	142	96	111	148	94	112	72	63	72	80	64	74	2.0	2.0
19 E.C.	174	108	130	148	78	101	147	80	102	162	105	124	150	80	103	149	81	104	86	60	64	90	72	76	2.0	2.0
Mean for 19 responsive patients#	185	107	133	164	94	117	163	94	117	186	110	135	158	96	116	153	92	112	80	69	69	84	74	73	2.2	2.8
Mean for 23 unresponsive patients	192	107	136	188	100	130	193	102	132	187	111	136	180	104	130	181	104	130	79	72	70	86	77	75	2.3	3.3

Key to table: S = Systolic blood pressure. D = Diastolic blood pressure. C = Control observations. M = Mean blood pressure. # = Reduction in mean blood pressure of 20 mm. Hg or more or to normotensive levels (below 150 mm. Hg systolic and 100 diastolic). ‡ = Treatment Period D_1—Observations made for first 2 months while receiving rescinnamine. * = Treatment Period D_2—Observations made during second to fourth month or longer while receiving rescinnamine.

TABLE 4B.—BLOOD PRESSURE RESPONSE TO RESCINNAMINE IN 42 PATIENTS WITH CONTROL DIASTOLIC PRESSURE MORE THAN 120 mm. Hg

Patients Group B		Supine Blood Pressure									Upright Blood Pressure									Pulse Rate						Dose Rescinnamine mg./24 hours	
		Control			Treatment Period D_1			Treatment Period D_2*			Control			Treatment Period D_1			Treatment Period D_2*			Supine			Upright				
		S	D	M	S	D	M	S	D	M	S	D	M	S	D	M	S	D	M	C	D_1	D_2*	C	D_1	D_2*	D_1	D_2*
1	Y.E.	226	133	164	210	115	147	237	122	160	202	137	159	189	115	139	217	123	154	60	63	57	71	70	60	2.0	4.0
2	F.A.	177	120	139	155	100	118	178	112	134	171	123	139	132	97	109	169	110	130	86	72	72	86	80	74	2.0	2.0
3	L.H.	219	128	158	203	114	144	187	104	132	231	136	168	206	126	153	193	109	137	100	87	64	96	77	67	2.0	4.0
4	H.A.	235	133	167	200	110	140	186	111	136	192	132	152	175	120	138	148	103	118	84	71	81	101	82	94	2.0	4.0
5	H.L.	221	114	150	190	100	130	222	114	150	213	129	157	191	119	143	208	123	151	65	61	68	86	62	70	2.0	4.0
6	B.R.	223	140	168	185	102	130	177	100	126	223	142	169	183	108	133	161	99	120	72	62	57	74	62	63	2.0	4.0
7	D.B.	192	134	153	166	112	130	180	119	139	189	136	154	158	117	131	171	124	140	96	74	79	98	85	99	2.0	4.0
8	H.C.L.	189	125	146	162	107	125	–	–	–	179	128	145	150	108	122	–	–	–	84	81	–	95	89	–	2.0	–
9	L.M.	239	127	164	223	113	150	206	111	143	221	128	159	216	107	143	184	102	129	80	69	68	84	72	73	2.0	4.0
10	L.H.	199	132	154	186	116	139	168	107	127	205	138	160	183	126	145	168	112	131	69	70	68	68	76	79	2.0	4.0
11	T.E.	188	108	135	175	93	120	175	92	120	185	126	146	157	97	117	155	89	111	82	70	68	95	85	81	2.0	4.0
12	McL.L.	175	117	136	161	99	120	152	104	120	187	124	145	153	101	118	157	105	122	94	78	89	90	91	85	2.0	2.0
13	S.D.	230	140	170	198	116	143	220	130	160	230	140	170	180	118	139	180	100	127	90	64	64	90	64	64	2.0	2.0
14	H.F.	190	130	150	190	120	143	160	98	119	174	124	141	160	110	127	158	90	113	80	76	76	80	76	76	2.0	2.0
15	R.F.	172	126	141	204	114	144	180	104	129	176	126	143	160	104	123	158	106	123	88	76	76	86	76	76	2.0	2.0
16	A.G.	240	140	173	270	110	163	260	120	167	230	150	177	246	116	159	210	118	149	100	62	62	100	62	60	2.0	2.0
17	D.T.	274	160	198	254	128	170	–	–	–	260	165	197	248	130	169	–	–	–	80	90	–	80	90	–	2.0	–
18	J.W.	210	110	143	190	100	130	150	100	117	190	120	143	150	100	117	150	100	117	68	56	56	66	55	53	2.0	2.0
19	S.A.	211	131	158	209	114	146	–	–	–	210	132	158	190	111	137	–	–	–	70	63	–	72	66	–	2.0	–
20	F.W.	208	128	155	160	100	120	155	100	118	210	120	150	160	100	120	155	95	115	84	80	76	80	78	78	2.0	2.0
21	M.B.	190	120	143	160	100	120	158	98	118	206	123	151	110	66	86	128	72	91	86	68	72	94	82	84	2.0	2.0
Mean for 21 responsive patients		210	128	155	193	109	137	186	108	134	204	132	156	176	109	132	171	104	127	82	71	70	85	75	74	2.0	3.1
Mean for 21 unresponsive patients		209	128	155	208	122	151	197	125	149	205	131	156	200	123	149	186	124	145	82	73	68	88	84	87	2.4	1.8

See Table 4A for key to abbreviations.

only in those patients with less severe disease.

The 2.0-mg. dose of rescinnamine appeared to produce nearly maximum reduction in blood pressure. The group of patients who were started on the 4-mg. dose is small (10 patients) but the response rate did not appear to be increased by using larger doses initially since only 2 of the 10 responded to this dose. When the dose of rescinnamine was doubled to 4 mg. daily at the end of 2 months, in 31 patients who previously received 2 mg., 15 (48%) were responsive. Seven of the responsive patients had failed to respond to 2 mg. but became responsive when the dose was increased to 4 mg. On the contrary, 2 patients who responded on the 2 mg. dose later became unresponsive while receiving the 4 mg. dose. Eight (25%) patients who showed a significant reduction on the 2 mg. dose showed an additional reduction of 10 mm. Hg or more in the upright position when the dose was increased. A similar response was noted in 4 patients (13%) when the blood pressures were taken in the supine position. The majority of the latter patients were in the more severely hypertensive group with diastolic pressures above 120 mm. Hg during the control period. Therefore, these latter observations suggest that rescinnamine may be slightly more effective in doses of 4 mg. than in doses of 2 mg. per 24 hours. However, these observations were certainly not conclusive.

TABLE 5.—INCIDENCE OF SIDE EFFECTS WITH RESCINNAMINE AS COMPARED WITH RESERPINE

	Rescinnamine				*Reserpine*			
	Period D_1		*Period D_2*		*Period D_1*		*Period D_2*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Number patients treated	84	100	64	100	62	100	47	100
*Side Response**								
Bradycrotic response	46	55	37	58	44	71	33	70
Sedation	29	35	15	23	29	47	13	28
Nasal Congestion	43	51	45	70	40	65	33	70
Increased Bowel Movement‡	23	27	7	11	3	5	3	6
Increased Appetite	26	31	12	19	37	60	28	60
Weight Gain	28	33	8	13	31	50	23	49
Fatigue and Weakness	34	40	22	34	27	44	23	49
Dizziness	13	15	9	14	13	21	3	6
Dreams	4	5	3	5	2	3	2	4
Impotence	3	4	2	3	0	0	2	4
Syncope	1	1	0	0	0	0	0	0

Key to table: * = Side Response indicates response other than blood pressure response, not necessarily an untoward effect.
‡ = One patient in this group had severe diarrhea for 3 weeks.
Period D_1 = Observations for first 2 months while receiving rescinnamine.
Period D_2 = Observations for 2 to 4 months or longer while receiving rescinnamine.

The side effects secondary to rescinnamine therapy are listed in Table 5. In none of the patients studied were these effects severe and they did not constitute a significant problem in therapy. A bradycrotic effect was produced in 46 (55%) of the 84 patients during Period D_1. This was defined as a reduction of the average pulse rate of 10 beats or more after treatment. The most frequent subjective complaint was that of nasal congestion which was present in 51% of the patients but this usually decreased in intensity within 2 months of continued therapy. The most troublesome side effects, though

TABLE 6.—SIDE REACTIONS AND SYMPTOMS IMPROVED (RESCINNAMINE AND RESERPINE)

	Rescinnamine						*Reserpine*					
		D_1			D_2			D_1			D_2	
Symptom or Sign Improved	*Total‡ No.*	*No. Improved*	*%*	*Total‡ No.*	*No. Improved*	*%*	*Total‡ No.*	*No. Improved*	*%*	*Total‡ No.*	*No. Improved*	*%*
1. Headache	53	37	70	46	37	80	22	16	73	15	14	93
2. Angina	8	5	63	8	8	100	2	1	50	2	1	50
3. Congestive failure	18	7	39	14	4	29	6	2	33	5	1	20
4. Electrocardiogram	63	6	10	50	3	6	37	2	5	28	6	21
5. Fundi	53	1	2	42	0	0	11	0	0	8	0	0
6. Renal impairment	30	4	13	21	4	19	14	0	0	10	1	10
7. Blood pressure	84	40	48	64	33	52	62	29	47	47	24	51
General Response												
—Good	28		33									
—Fair	41		41									
—Poor	15		15									

D_1 = After receiving drug for 2 months.
D_2 = After receiving drug for 4 months or more.
‡ = Total number of patients with symptoms prior to therapy.

somewhat less frequent, were weakness, fatigue, and drowsiness. These symptoms developed in about 40% of the patients and presented the most nearly incapacitating side effects of all. Weakness was occasionally described as being confined to the lower extremities, but generally constituted a true depression of vigor and drive. Sedative effect was closely associated with weakness and was next in frequency of occurrence. As with most other side effects, this symptom also regressed in intensity on prolonged treatment. Thirty-one per cent of the patients noted an increase in appetite on rescinnamine therapy in contrast to 60% during a comparable initial period on reserpine therapy. Increased appetite was usually associated with weight gain and the incidence was the same. Both complaints were reduced to about 15% to 20% on prolonged therapy with rescinnamine.

Increased bowel movements constituted a definite response to treatment in 27% of the patients during the first 2 months of therapy but only one patient had frank diarrhea. During the second 2-month period, only 11% of the patients noted increased bowel movements. Other side effects noted less frequently were dizziness, impotence, syncope, and unusual dreams. Dizziness was not due to postural changes. Nasal congestion was the only troublesome side effect which increased in frequency during the second 2-month period of therapy despite an increase in the dose of rescinnamine. This complaint, though increasing in frequency, was usually of less intensity during the second period.

For the most part, the side effects previously observed with reserpine appeared in approximately the same order and frequency with rescinnamine. There were, however, fewer reports of an increase in appetite, and therefore, weight gain, with rescinnamine than

with reserpine. The bradycrotic response was not only less frequent with rescinnamine than with reserpine, but the degree of reduction was much less. Also the incidence and intensity of sedation was less with rescinnamine.

Table 6 lists the symptoms and physical findings improved after 2 and 4 months of rescinnamine therapy. Relief of headache occurred in most patients, (70% after 2 months and 80% after 4 months) who had this complaint during the control period. Although headaches were for the most part due to hypertension, a few patients gained relief of this complaint who did not describe frank hypertensive headaches. Only 8 of all the patients studied complained of angina but of this group, 63% were relieved at the end of 2 months and 100% relieved after 4 months of rescinnamine therapy. Eighteen patients were in congestive failure during the control period; about one-third of these were improved by reduction of blood pressure on rescinnamine therapy. These patients had no other alterations in the usual maintenance regimen for cardiac decompensation. Significant electrocardiographic changes were present in 63 of the 84 patients studied before therapy. Of these, only 6 showed improvement at the end of the 2 months and 3 out of 50 had electrocardiographic evidence of return of T waves toward normal at the end of 4 months. These were patients who initially showed electrocardiographic evidence of myocardial ischemia. There was also evidence of improvement in renal function, 13% after 2 months and 19% improvement after 4 months. Here again, the improvement was effected in those patients who had early renal arteriolar changes. Definite improvement in hypertensive eye ground changes was clear-cut in only one patient.

Discussion. PHARMACOLOGY. Rescinnamine[1] apparently reduces the blood pressure in the same manner as reserpine, that is, by central depression of the sympathetic nervous system. These deductions are based primarily on laboratory evidence. For example, stimulation of the central end of the severed vagus which carried afferent impulses to the brain, ordinarily produces a sharp rise in blood pressure. However, when rescinnamine is given, this vasopressor response is blocked. Likewise, the rise in blood pressure that is usually seen with hypoxia is also blocked as is the carotid sinus reflex. At the same time, there is no evidence of peripheral blockade of the sympathetic nervous system since stimulation of the splanchnic nerve produces the same results after rescinnamine therapy as are observed in animals who have not received rescinnamine. The blood pressure response to norepinephrine is essentially unchanged. This indicates an absence of peripheral blockade of the sympathetic nervous system. Cardiac output is not affected by rescinnamine[1].

When administered orally, neither rescinnamine nor reserpine produces a postural reduction in blood pressure, that is, the reflexes remain intact when changing from the supine to the upright position. However, this may be merely a matter of dosage since if adequate doses of rescinnamine are given parenterally, there is frequently an orthostatic effect on blood pressure. According to the current observations, rescinnamine has less slowing effect on the heart than does reserpine and apparently has less gastrointestinal effect. Likewise, the sedative effect is less marked in the case of rescinnamine.

Although rescinnamine, when administered orally, is only moderately effective as a hypotensive agent, when given by the parenteral route, reduction in blood pressure is a consistent response. Our observations in these patients

would indicate that an equal reduction in blood pressure can be obtained with rescinnamine as with reserpine but a somewhat larger dose must be used (ratio between 1:1 and 2:1).

CLINICAL OBSERVATIONS. The present study proves the antihypertensive effect of rescinnamine and indicates that there is more than one active hypotensive alkaloid in *Rauwolfia serpentina*. The antihypertensive effect is particularly apparent by the blood pressure response observed after parenteral administration of rescinnamine, which was equally as pronounced as the response to parenteral reserpine, observed in this and in previous studies[3]. There were minor differences in the response to parenteral administration, however, which warrant mention. The optimal dose of reserpine for most patients was 5 mg. given parenterally. This difference was actually the most significant between the two drugs. The two alkaloids of *Rauwolfia serpentina* are quite similar in their antihypertensive activity and in their side effects. The action of both drugs is mild, and slow in onset, but that of rescinnamine slightly more delayed than the onset of action of reserpine. The maximum hypotensive effect after rescinnamine occurred during the 5th and 6th hours after parenteral administration of the drug while with reserpine the maximum response usually occurred during the 3rd and 4th hours after administration. At the time of maximum blood pressure reduction there was a tendency to postural hypotension (Figs. 1 and 2). In patients who developed severe hypotension after either drug the response to norepinephrine or Vasoxyl* was immediate. Concurrently with the slower onset of action of rescinnamine, the total duration of hypotensive effect seemed to be greater after rescinnamine than after reserpine.

The side effects attending the parenteral administration of rescinnamine and reserpine were essentially the same; somnolence, dizziness, weakness and nasal congestion were prominent to about the same degree after both drugs in two separate groups of patients studied.

Rescinnamine administered orally is only moderately potent in its effect on blood pressure, but by this characteristic, as with reserpine, it provides a safe, easily tolerated agent for chronic drug administration, either alone or in combination with more potent antihypertensive agents. The dosage and results with rescinnamine and reserpine given orally are even more similar than those observed following parenteral administration. The average daily oral doses of rescinnamine in 84 patients were 2.5 mg. and 3.0 mg. for periods D_1 and D_2 respectively. The doses of oral reserpine in 62 patients previously studied were similar. Of the 84 patients treated for 2 months (Period D_1) on oral rescinnamine, 47% showed a significant blood pressure reduction at the end of the period. Of the 64 patients treated for 4 months or more (Period D_2), 52% had a significant blood pressure response. In 62 patients receiving reserpine for 2 months, 47% also responded by the end of the first period (Period D_1). Forty-seven patients were then followed for 5 months or longer with significant reduction in pressure occurring in 51% at the end of this time (D_2).

Although the over-all incidence of side effects associated with oral administration of rescinnamine and reserpine were essentially the same, statistical analysis showed certain differences which may serve as a guide in the future selection of antihypertensive drugs of this group. The bradycrotic response after rescinnamine was less

*Methoxamine was furnished by Burroughs-Wellcome & Co.

frequent and less pronounced than that previously noted after reserpine. The sedative effect after rescinnamine was also less frequent and less pronounced. This was particularly obvious during the first 2 months of therapy. Nasal congestion was equally frequent and intense after both drugs. Increased bowel movements were 2 to 5 times more frequent after rescinnamine than after reserpine. This was never considered a truly disturbing side effect, but actually a helpful agent in the relief of the chronic constipation that is usually present in most hypertensive patients. Increased appetite and weight gain were 2 to 3 times more frequent after reserpine than after rescinnamine. Fatigue and weakness were about as frequent after both drugs but these were more pronounced after reserpine.

Summary and Conclusions. 1. Twenty-six hypertensive patients received parenteral rescinnamine in doses ranging from 2.5 to 15 mg. Blood pressure response and evaluation of side effects established the optimal dose to be 10 mg. when given parenterally. Of 20 patients who received this dose, 90% demonstrated a significant reduction in mean arterial pressure within 5 hours after administration of the drug. Seventy per cent became normotensive.

2. Eighty-four hypertensive patients received oral rescinnamine on an outpatient basis over a period of 2 to 4 months or more. Forty-seven per cent of the 84 patients treated for 2 months demonstrated a significant reduction in pressure at the end of this time, while 52% of those treated for 4 months or more showed a significant reduction in mean arterial pressure. The response to the drug was not necessarily dependent on the severity of the hypertension, but of the patients who became normotensive, only 3 were from the group with the more severe hypertension.

3. Rescinnamine, a pure alkaloid of *Rauwolfia serpentina*, has been shown to be equally as effective in the reduction of blood pressure as the initially introduced alkaloid, reserpine. Its administration is accompanied by much the same qualitative side effects as noted after reserpine, though severity of some side effects was less.

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(Interlingua on page 596)

CLINICAL EVALUATION OF ACENOCOUMARIN, A NEW 4-HYDROXYCOUMARIN ANTICOAGULANT

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Since the introduction of Dicumarol into the field of clinical medicine, there has been a constant search for another 4-hydroxycoumarin derivative which would show greater safety and effectiveness in thromboembolic disorders. The principal disadvantage of Dicumarol has been its delay of 49 to 96 hours in producing a therapeutic hypoprothrombinemic state. In addition, because of its slow excretion, therapeutic levels are difficult to anticipate. This has frequently led to inadequate hypoprothrombinemia, false sense of security, prolonged and expensive period of heparin therapy, unforeseen hemorrhagic problems, and fear on the part of the physician to use anticoagulants when they are indicated.

Tromexan appeared to obviate these disadvantages because of the rapidity with which it produced hypoprothrombinemia (18 to 24 hours) and its rapid rate of metabolism. The drug, however, is administered twice daily to be therapeutically effective because of the property of rapid metabolism. Moreover, larger doses are required than with Dicumarol because of lesser potency.

It is apparent that a drug of greater potency than Tromexan but with its rapid action in producing hypoprothrombinemia, would be an improved medication. A drug with a slightly more delayed excretion than that of Tromexan would also be desirable. Thus a single daily dose should maintain a state of therapeutic hypoprothrombinemia, and, upon withdrawal of the drug, the prothrombin should rapidly return toward normal. The anticoagulant should also be safe and easy to administer, consistent in its action, and inexpensive. It is the purpose of this paper to describe the characteristics of acenocoumarin* (nitro-phenyl-acetyl-ethyl-4-hydroxycoumarin) in its clinical application as an anticoagulant (Fig. 1).

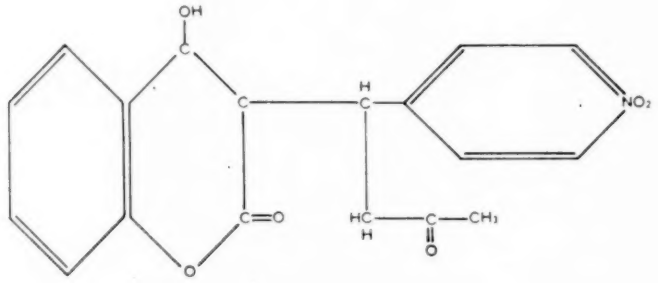
Method and Material. Sintrom is a white crystalline, tasteless powder which was supplied as 4 mg. scored tablets and 2 mg. capsules. The drug was administered in a single oral dose at 2:00 P.M. each day. This was 6 hours following withdrawal of the daily blood for prothrombin determination. Initial prothrombin, blood urea nitrogen determinations and urinalysis were performed on patients before or at the time of the first dose of Sintrom administration.

The Link-Shapiro modification of Quick's method of prothrombin determination with whole plasma and a 12.5% dilute plasma was the technique used in our study[1]. The thromboplastin was Simplastin. The therapeutic

*Sintrom brand of acenocoumarin was made available to us for clinical study by Geigy Pharmaceuticals, New York, New York.

level of hypoprothrombinemia was considered to be a value of 2 to 3 times the normal dilute plasma prothrombin time.

This report is based on observations of 65 patients with thromboembolic conditions who were treated with Sintrom for 1,762 patient days, an average of 27 days per patient. A total of 85 patients was treated for 2,065 patient days, but all patients who were treated less than 12 days or who had infrequent prothrombin determinations (those treated as outpatients) were omitted from this clinical evaluation study. Table 1 shows the clinical condition which prompted the use of anticoagulant therapy.



NITRO-PHENYL—ACETYL-ETHYL—4 HYDROXYCOUMARIN
(SINTROM)

Fig. 1.

CLINICAL APPLICATION. Heparin was used during the first 24 hours of anticoagulant therapy in 8 patients with acute myocardial infarction. The initial single oral dose of Sintrom was 20 mg. the first day; however, patients with evidence of hepatic dysfunction, cardiac or renal insufficiency, and malnutrition, received a smaller dose. For example, 2 patients with blood urea nitrogen values greater than 30 mg. per 100 ml. received 16 and 8 mg. respectively as the initial dose. Forty-eight of the 65 patients received 20 mg. of Sintrom initially and 8 to 16 mg. on the second day. In general, the second dose could be estimated with some degree of accuracy from the response of the prothrombin time to the initial dose. During the first 48 hours, the therapeutic range was not exceeded by this method of initial dosage evaluation. The average dose required to maintain the therapeutic range was between 4 and 6 mg. per day. One patient with thrombophlebitis required 14 mg. per day. Another patient required as little as 0.5 mg. per day. She was a young female with multiple pulmonary emboli, secondary to severe rheumatic carditis with congestive heart failure. The doses given are summarized in Table 2.

TABLE 1.—INDICATIONS FOR ANTICOAGULANTS

Diagnosis	*No. of Patients*
Acute myocardial infarction	35
Thrombophlebitis	17
Pulmonary emboli	10
Postoperative prophylaxis	3

Fifty-five of the 65 patients (85%) with thromboembolic disorders were within the therapeutic range of hypoprothrombinemia in 48 hours or less after the initial dose of Sintrom. Five patients developed therapeutic hypoprothrombinemia between 12 and 24 hours after the initial dose. These 5

patients continued to show greater than average sensitivity to the drug during the maintenance period. The results are summarized in Table 3.

Sintrom was given to 5 patients free of hepatic or renal dysfunction and without thromboembolic disease. Initial and frequent prothrombin determinations were obtained to demonstrate the effect of a single oral 20 mg. dose. Their response to the drug as judged by the dilute plasma prothrombin time is shown in Fig. 2. It indicates that a maximal increase in prothrombin time develops in approximately 32 hours and rapidly returns toward normal thereafter. A second group of 5 individuals were given 16 mg. of Sintrom 24 hours after the initial 20 mg. dose. The effect of the two doses on the dilute plasma prothrombin time is shown in Fig. 3. The second dose effected a marked and more sustained increase in prothrombin time, lasting 32 to 56 hours after the initial dose was administered. The prothrombin time rapidly returned toward normal approximately 30 hours after the second dose.

Three patients of the group of 65 with thromboembolic disorders, received vitamin K or K_1 preparations for treatment of excessive hypoprothrombinemia and are briefly discussed below.

TABLE 2.—DOSES OF G23350 (SINTROM)

Total Dose mg.	*Initial Dose No. of Cases*	*Second Day Dose No. of Cases*	*Av. Maintenance Dose No. of Cases*
24	1		
20	48	1	
16	13	2	
14			1
12	1	25	
10	1	10	
8	1	20	4
7			5
6		2	9
5			16
4		4	9
3			10
2		1	10
0.5			1

TABLE 3.—TIME REQUIRED FOR THERAPEUTIC EFFECT

Interval Before Attainment of Therapeutic Range (Hours)	*No. of Cases*
12–18	3
19–24	2
25–36	12
37–48	38

Case Reports. CASE 1. A 56-year-old male with an acute myocardial infarction had a dilute plasma prothrombin time of 101 secs. the day he received a 4 mg. dose of Sintrom. His prothrombin time rose to 190 secs. the following day and a minor epistaxis occurred. The drug was withheld and 50 mg. vitamin K_1 emulsion was given intravenously. Subsequent prothrombin times, taken every 24 hours, were normal for 4 days in spite of reinstitution of Sintrom administration.

CASE 2. A 24-year-old female with multiple pulmonary emboli and severe cardiac insufficiency from rheumatic heart disease, developed excessive hypoprothrombinemia (dilute prothrombin time 163 secs.) without evidence of hemorrhage. Sintrom was withheld and she was given 50 mg. vitamin K_1 emulsion intravenously which restored the dilute prothrombin time to a therapeutic level within 18 hours in spite of severe cardiac cirrhosis of the liver.

CASE 3. A 60-year-old male developed a dilute plasma prothrombin time of 168 secs. during the 7th day following an acute myo-

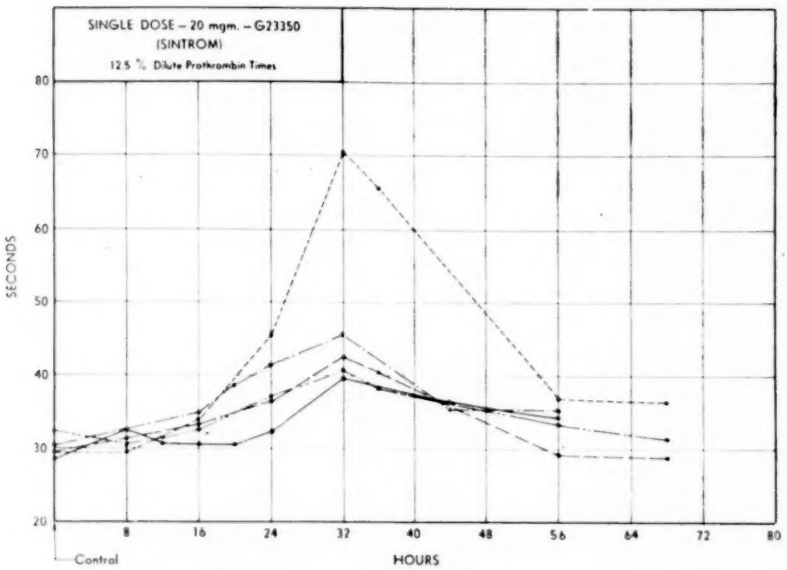


Fig. 2.—Twenty milligrams of acenocoumarin administered to 5 patients at the time of the control dilute prothrombin time.

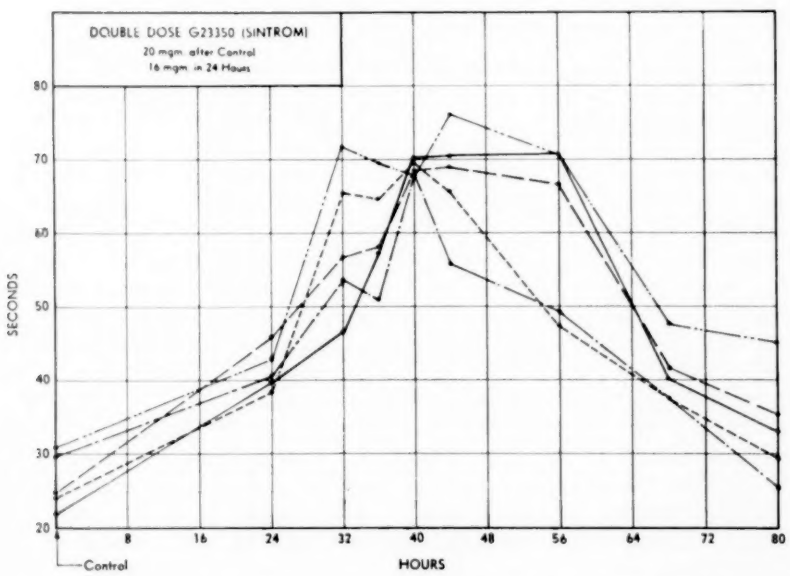


Fig. 3.—Twenty milligrams of acenocoumarin administered to 5 patients at the time of the control dilute prothrombin time; 16 mg. administered 24 hours later.

cardial infarction. Sintrom was withheld, and he was given 72 mg. of water-soluble vitamin K to return prothrombin values to the therapeutic range. It is not certain how efficacious water-soluble vitamin K was in this case, since his prothrombin time had not returned to a therapeutic level within 24 hours or less as in the previous case cited.

Discussion. Depending upon the thromboembolic lesion requiring anticoagulant therapy, heparin may still be desirable to produce an immediate anticoagulant effect. It is apparent from this study that this would be needed for a period of approximately 24 hours. By this time, the majority of patients would be approaching adequate hypoprothrombinemia after an initial oral dose of 20 mg. of Sintrom. Even when a suitable 4-hydroxycoumarin derivative has been given intravenously, a therapeutic hypoprothrombinemia has not been achieved in less than 24 hours in the majority of patients.

The initial dose of 20 mg. of Sintrom appears to be satisfactory for most patients. Since this was an original clinical experience with a new drug, initial doses larger than 20 mg. were not used. It may be possible to produce a more rapid hypoprothrombinemia with larger doses. We believe that in the presence of renal or hepatic insufficiency and malnutrition smaller initial doses are desirable, for example, 12 to 16 mg. Such patients are apt to require smaller amounts of the drug for maintenance, for example, 1 to 2 mg. as compared to 4 to 6 in patients without these complications.

All patients developed adequate hypoprothrombinemia from Sintrom. The administration of a single daily oral dose produced an adequate hypoprothrombinemia which appeared to be well sustained according to daily prothrombin values. On single daily doses of Sintrom 65 patients were within the therapeutic range of hypoprothrombinemia (as judged by the dilute plasma prothrombin times 18 hours after the daily dose) approximately 75% of the time, and we would anticipate better results with further experience. It is noteworthy that this drug was mainly administered by the medical house staff, none of whom had had extensive experience with anticoagulant therapy. We consider this to be significant evidence for the effectiveness and ease of Sintrom administration.

Excessive hypoprothrombinemia developed in 3 patients during maintenance therapy. One of these patients had a bout of epistaxis but the other two had no evidence of hemorrhage. Excessive hypoprothrombinemia responded to vitamin K and K_1 in these 3 patients. We believe that unless there is evidence of bleeding due to excessively prolonged prothrombin time, that the drug should be withheld rather than give vitamin K_1. Withholding the drug usually prevents the loss of therapeutic hypoprothrombinemia. It also obviates the presence of a sustained normal prothrombin state which usually occurs following vitamin K_1 and which is frequently irreversible for several days.

After cessation of Sintrom the dilute prothrombin time rapidly approaches normal within 30 hours. This has obvious advantages in patients requiring emergency surgery or when excessive hypoprothrombinemia has occurred.

There was no evidence that the drug caused gastrointestinal irritation nor hepatic, renal, or hemopoietic toxicity as judged by clinical and laboratory observations.

Summary. 1) The clinical application of a new oral 4-hydroxycoumarin anticoagulant, Sintrom, is presented. Sixty-five patients treated with Sintrom brand of acenocoumarin were observed daily for an average period of 27 days and represent the clinical evaluation of the drug.

2) Effective drug doses were found

to be 20 mg. the first day, 8 to 16 mg. the second day, and an average of 4 to 6 mg. for maintenance therapy.

3) Vitamin K_1 appears to be effective in reversing excessively prolonged prothrombin times due to acenocoumarin, as with other coumarin anticoagulants.

4) Sintrom appears to have certain advantageous characteristics. These features are: effectiveness in small single daily oral doses, absence of untoward side effects, and ease and safety of maintaining therapeutic anticoagulation.

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SUMMARIO IN INTERLINGUA

Evalutation Clinic de Acenocoumarina, un Nove Anticoagulante Derivate de 4-Hydroxycoumarina

1. Es presentate le application clinic del nove anticoagulante oral Sintrom que es un derivato de 4-hydroxycoumarina. Sexanta-cinque patients tractate con le marca Sintrom de acenocoumarina esseva observate diurnemente durante un periodo median de 27 dies. Iste observationes representa le base del evaluation clinic del droga.

2. Esseva constatate que dosages efficace amonta a 20 mg le prime die, 8 a 16 mg le secunde die, e un quantitate median de 4 a 6 mg per die como therapia de mantenentia.

3. Il pare que vitamina K_1 ha le effecto de reverter excessivemente prolongate tempores prothrombinic causate per acenocoumarina como in le caso de altere anticoagulantes coumarinic.

4. Il pare que Sintrom ha certe characteristicas avantagiose. Iste characteristicas es: efficacia in parve oral doses diurne unic, absentia de negative effectos lateral, e facilitate e securitate in mantener anticoagulation therapeutic.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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RECENT CONTRIBUTIONS TO DIURETIC THERAPY

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MANY new drugs have been synthesized, screened in animals, and tested in man in the search for new diuretic agents, and special attention has been paid to the matter of increased potency, reduced toxicity, diminished disturbance in the electrolyte balance, and wide clinical applicability. While considerable progress has been made, there remains much room for improvement. There have been several critical reviews of the mountainous literature. The reader may refer to the full historical and clinical account by Vogl[371], a shorter one by Schroeder[313], and one on the more technical aspects by Pitts and Sartorius[282] for the publications up to about 5 or 6 years ago. The present report is confined to the papers subsequent to these, papers which have appeared between 1950 and 1955, with only an occasional reference to older works. The reports are abstracted under two general headings, the clinical conditions in which diuretic therapy has been applied, and the pharmacology of the specific agents.

Clinical Experiences. The diuretic drugs now in common use are applied to a number of clinical conditions. Of these, the relief of edema and particularly that of heart disease is by far the most important. They are also used in the ascites of cirrhosis, the nephrotic syndrome, and the edema of pregnancy. Recent trends in this field are summarized in a recent Cornell Conference on Therapy[61], and in reviews by Blumgart[29], Burch[40], Kattus[180], Stroud and Stroud[353] and the late F. R. Schemm[309]. Reference to the special aspects of the treatment of left heart failure may be found in the review by Lombardo and Harrison[208] and of the problem of congestive heart failure in children by Logue and Hurst[207]. The hazards in the treatment of congestive heart failure have been summarized by Altschule[3]. Glaucoma, bromide intoxica-

tion, the anginal syndrome, epilepsy and pre-menstrual depression provide highly specialized uses for diuretics in conditions in which edema is not present or at least not definitely established.

ELECTROLYTE DISTURBANCES INHERENT IN DIURETIC THERAPY. Diuretic drugs are almost always applied for the removal of extracellular fluid. Regardless of the nature or the site of their action, if diuretics are to accomplish this they must induce a negative sodium balance[276,321,322,336]. Since this action is never specific for sodium alone but to a varying degree involves other ions as well, diuresis constitutes a variable threat to electrolyte homeostasis. It appears not to matter greatly what the precise nature of the diuretic device is, restriction of sodium in the diet, mercury inhibiting salt resorption in the renal tubule, acetazolamide depressing hydration of carbon dioxide, exchange resins drawing salt from the food in the intestinal tract, or water diuresis[302], all may and sometimes do induce clinically evident electrolyte disturbances. Combinations of these devices are even more likely to do this[62,166,339]. Such disturbances have also been reported after the removal of edema fluid of cirrhosis by aspiration[167,262].

Electrolyte disturbances are, therefore, inherent in the nature of diuretic action and to that extent this danger is inseparable from the relief of edema. The subject has been summarized well by Danowski and coworkers[66,73]. Detailed descriptions of the various syndromes which may develop have been published by many[3,113,166,265,315,339,341,342,387].

EDEMA OF HEART DISEASE. The rationale for the use of diuretics for the relief of the edema of heart disease correlates with our understanding of the mechanism of its development. Additions to our knowledge regarding its genesis may not only explain successes and failures but also lay the groundwork for new drugs and more effective regimens of treatment. For example, acetazolamide (Diamox) might not have been tried as a diuretic had not the connection between the activity of the enzyme, carbonic anhydrase, and sodium excretion been known in 1940 when it was also noted that sulfanilamide produced an alkaline urine[217].

Unfortunately for the case of more rapid progress in its therapy, there is yet no entirely satisfactory explanation of the mechanism of development of cardiac edema. Defects are recognized in the more modern "forward-failure" concept as well as in the older and less commonly accepted "backward failure" concept. Albert, Smith and Eichna[2] suggest that, whereas clinical manifestations may suggest a uniformity in the mechanism of cardiac edema, there is evidence that more than one mechanism for the development of cardiac edema may exist. Attempts to close the gaps in our understanding of this common symptom form a substantial chapter of medical literature[41,43,66,78,239,242,263,276,321,322,336,345,346,382,399]. While limitations of space permit only brief consideration of this problem here, it is important insofar as it may indicate the direction which newer approaches to the therapy of cardiac edema will take.

The Primary Disturbance. While there is general agreement that in congestive heart failure there is retention of sodium, with water held for isoosmotic reasons[276], opinions on how this comes about are varied and there are also contrary opinions, such as those of Miller[245], that the sodium retention may come on the heels of primary water retention. Studies of the electrolyte concentrations of tissues and body fluids in congestive heart failure have

not settled this issue[88,113,172,173,174,245,315,322,341,342].

Hemodynamic Mechanisms. The origins of the more commonly held modern view[242,346,382] that the sequence of events which, in heart disease, leads to edema, starts with diminished cardiac output are usually credited to Starr *et al.*[345], who in 1943 challenged the then current view that increased venous pressure was the dynamic disturbance in heart disease which caused the edema. Decreased cardiac output has been demonstrated in the patients with the edema of heart disease but it is not invariable[321]. McMichael[239] states that edema may develop at any level of cardiac output at rest, and high output failure is a well recognized clinical entity[400]. Eichna and coworkers[88] studied changes during the process of compensation of congestive heart failure. They found that, while in general, there was improvement of cardiovascular and renal function which was regularly followed by alteration, toward normal, of blood volume and electrolyte excretion, these changes did not so regularly include increases in cardiac output, renal plasma flow or glomerular filtration rate. These findings suggest that the latter disturbances are not essential to the development of cardiac edema.

Intrarenal Mechanisms. Reduced renal blood flow, reduced glomerular filtration rate, increased sodium resorption and, finally, increased water retention have been suggested by Merrill[242], as well as by many others[346,382] as the chain of events leading to the development of cardiac edema. Hiller and Jacobson[163] found reduced renal blood flow before the appearance of signs of congestive heart failure. They suggest that this renal ischemia is due to efferent arterial spasm which results in reduced glomerular filtration. No proof for this hypothesis is offered and Grossman *et al.*[150] observe that there is no evidence of renal redistribution of blood in congestive heart failure. Chalmers, Lewis and Pawan[52] found that a dissociation between glomerular filtration rate and the rate of sodium excretion was possible and suggest that other unidentified factors may be involved.

Maxwell, Breed and Schwartz[230] observed increased renal venous pressure, reduced renal blood flow and glomerular filtration rate, with reduced excretion of sodium, potassium and chloride in man but the rise in venous pressure was not of sufficient magnitude to cause the renal ischemia observed. Hwang *et al.*[171] found an initial correlation between increased venous pressure and reduced glomerular filtration rate in the dog but, in view of later compensatory changes, felt that they had failed to establish a direct relationship between intrarenal venous pressure and sodium excretion. Newman[263], studying reactions to exercise, noted elevation of venous pressure which developed to a much greater degree in patients with congestive heart failure than in the normal and felt that the evidence indicated that the elevation in intrarenal venous pressure might be the stimulus to sodium retention. Judson[177], on the other hand, found that there was a discrepancy between the effects of exercise in patients with congestive heart failure on glomerular filtration and sodium resorption which was suggestive of an alteration in tubular activity, a concept supported by Duncan[86].

Hormonal Mechanisms. The possibility of hormonal disturbances has been suggested with increasing frequency[22,125,242,285,322,399]. The antidiuretic hormone and its role in the metabolism of salt and water have been reviewed in considerable detail by Pickford[278] and by Verney[369].

Antidiuretic materials appear in the urine under a variety of circumstances, for example, in normals after smoking[360], but they are reported in greater than usual amounts in the urine and plasma of patients with the edema of heart disease, liver disease and kidney disease[21,74,77,286,332,347,355,392]. Not all are agreed that these findings bear any relationship to the edema of heart disease. While they could demonstrate differences in the antidiuretic activity of the sera of patients with congestive heart failure and of normals, Perry and Fyles[275] found no consistent differences and concluded that antidiuretic activity was not responsible for the edema. White, Rubin and Leiter[392] also do not support the contention that edema of heart disease may be due to overproduction of an antidiuretic hormone.

Lasche, Perloff and Durant[193] suggest that hormones of the adrenal cortex may play a role either in the development or the maintenance of the edema of congestive heart failure. In a series of studies, Luetscher and Curtis[211,212,213] have identified a mineral-retaining corticoid, aldosterone, as consistently present in amounts significantly greater than normal, in the urine of patients with congestive heart failure, the nephrotic syndrome and cirrhosis. These observations are supported by the work of Liddle *et al.*[204]. The nature of the stimulant to the increased production and liberation of aldosterone has not been elucidated although Laragh and Stoerk[192] suggest that potassium is the primary regulator.

Liver. Selkurt[322] points out that in advanced congestive heart failure hepatic damage secondary to the circulatory changes may contribute to the further development of edema. Snavely[337] suggests a more positive role for the liver in salt and water metabolism, that in congestive heart failure the liver may initiate increased activity of salt-retaining materials but there has been no confirmation of this view.

Treatment. The treatment of congestive heart failure has not changed appreciably in the past 6 years. While results obtained with diuretics have been satisfactory in the hands of most clinicians and the agents used are more or less the same, views relating to the best approach to the relief of edema are still being argued[3,40,180,207,208,313,315,353]. These are so well-known that they will not be repeated here. More fruitful attention has been given recently to the problem of the so-called refractory edema of heart disease.

REFRACTORY EDEMA OF HEART DISEASE. This is a term with inconstant implications, changing largely in inverse relation to the effectiveness of measures applied. With the advent of modern diuretics, the incidence of refractory edema has diminished markedly and is said by Rubin *et al.*[303] now to comprise less than 1% of patients with congestive heart failure. In a recent conference (unpublished Cornell Conference on Therapy) refractory cardiac edema was defined as that which a routine of daily 2 ml.-doses of mercurial diuretics together with digitalis and salt-poor diet failed to relieve.

Although an accurate diagnosis is always suggested, the major emphasis has been laid on the possibility of disturbances of electrolyte homeostasis in these cases[283,344]. Others have noted that electrolyte imbalance was very infrequently found to be the cause of resistance to routine therapy with mercurials[303]. Blumgart[29] points out that there are many causes for refractoriness and among these he emphasizes hypoproteinemia.

Aminophylline. Vogl and Esserman[372] claim that the addition of aminophylline to a regimen of mercurial diuretics enhances the circulation of the kidney

and potentiates the action of the mercury. They suggest that this phenomenon is useful in "intractable" edema although they admit that "complete lack of response to mercurial diuretics has never been demonstrated." Their data show that patients in their study were inadequately treated with mercurial diuretics. The utility of the method requires confirmation.

Resins. Kleiber and Pickar[186] describe "encouraging" results in "intractable" cardiac failure. Their patients received so little mercurials that the edema should not be considered "intractable." There is the suggestion by Bonner[31], Elkinton *et al.*[89], and Friedman[116] that the resins may act to potentiate mercurial diuretics, especially in those cases in which a hydrogen exchange resin is used to the extent of inducing a degree of hyperchloremic acidosis.

Ammonium Chloride. Ammonium chloride may synergise with mercurial diuretics[143,164]. Batterman[12] reports, without explanation, that this does not apply equally to all mercurial diuretics. Stapleton and Harvey[374] found that ammonium chloride may reverse refractory heart failure due to hypochloremia. However ammonium chloride may assist in the action of the mercurial diuretics, it does not appear to provide a consistent answer to the problem of refractory edema. Further support of the action of mercurials is usually required[303].

Acetazolamide (Diamox). Maren[219] indicated that in dogs serial use of acetazolamide (Diamox) and mercurials resulted in enhancement of diuresis. Rubin *et al.*[303] used this device in the management of refractory edema, but found that only after Diamox was combined with relatively large doses of ammonium chloride, so that a degree of hyperchloremic acidosis developed, was the lost vigor restored to the mercurials. They describe treatment in which courses of Diamox are alternated with courses of ammonium chloride and mercurial diuretics.

Cortisone and ACTH. Schemm and coworkers[48,158] described 20 cases of otherwise refractory edema in which, following the use of corticotropin (ACTH) and cortisone, sodium excretion and diuresis returned spontaneously in 7, while in 11 there was restored responsiveness to mercurial diuretics. The authors are unable to describe the type of patient with resistant edema who is likely to respond to this form of therapy. This paradoxical phenomenon lacks not only explanation but also confirmation.

Peritoneal Dialysis. Leiter[199] described peritoneal dialysis as a means of removing sodium. This procedure is followed by diuresis in some patients with resistant cardiac edema, but the physical factors involved in its application seem to have limited its utilization.

Southey-Leech Tubes. A plea for the use of this device has been made by Fiese and Thayer[104] who claim that it is more sound, physiologically, than diuretics in that it removes edema *per se* and does not act through the nonspecific diuresis of electrolyte. Although no cases of electrolyte imbalance have yet been reported as a result of the use of the Southey-Leech tubes this may be so only because the method is so little used. Electrolyte disturbances have been reported following abdominal paracentesis[167,262] and, on the same basis, it seems probable that it could occur after the mechanical removal of interstitial fluid.

Diet. Diets with low salt content have long been used in combination with diuretics, especially for resistant cases. Iseri *et al.*[172,173] have described satisfactory results with diets containing as little as 50 mg. sodium. The

Council on Foods and Nutrition of the American Medical Association[62] has issued a warning about the possibilities of salt-depletion syndromes resulting from low-salt diets used in combination with potent diuretic agents.

NEPHROTIC SYNDROME. Since the report in 1941 by Tyson of fatalities following the use of mercurial diuretics in children with the nephrotic syndrome, this condition has been an accepted contraindication to their use, even though the danger has never been confirmed by others.

Cortisone and ACTH. Heidorn, Schemm and Layne[159] report good results in the therapy of the nephrotic syndrome and provide details of its influence on sodium, and water and electrolyte loss as also do Luetscher and his coworkers[214,215,216], Merrill and Wilson[243] and Riley[296]. Barnett *et al.*[7,8] argue that in many cases in which diuresis is induced, there are indices of improvement in renal function along with the relief of edema and that this may well indicate a salutary effect on the basic disease process. At the time of the publication (1954) they suggested that cortisone was the agent of choice[7].

Thorn *et al.*[362], reporting effective use of cortisone and ACTH in the nephrotic syndrome, found that there was no over-all beneficial action in any form of nephritis. Rapaport *et al.*[287] describe a temporary remission after ACTH in 28 of 34 children with the nephrotic syndrome which was unrelated to age, duration, severity or such signs of renal disease as hematuria, azotemia, hypertension and improvements in biochemical derangements. These authors expressed doubts whether the ultimate course of the syndrome was permanently or significantly influenced by the therapy, pointing out that even striking improvements were often short-lived and sometimes associated with disagreeable or more serious reactions. Frenkel, Groen and Hellings[112] report that, in one patient, cessation of ACTH administration was followed by acute arthralgia. Boyd and Commons[33] are uncertain about the advisability of this form of therapy for the nephrotic syndrome mainly because, in addition to the absence of good evidence that it makes much difference in the eventual result, there appear to be real hazards to the therapy.

Resins. Lippman[206], Mateer *et al.*[228] and Payne and Wilkinson[270] report that the exchange resins may remove edema in the nephrotic syndrome but warn against the possibility of electrolyte disturbance and inducing other forms of renal dysfunction.

Albumin. Luetscher *et al.*[215] report that concentrated human albumin may be used effectively in the nephrotic syndrome, that it elevates colloid osmotic pressure and increases glomerular filtration rate and water excretion. Orloff, Welt and Stowe[266] found that salt-poor serum albumin produced a diuresis in patients with the nephrotic syndrome. They indicate that the effect is greatest in those with the lowest serum albumin levels but found no significant changes in electrolyte or consistent alteration in glomerular filtration rate.

CIRRHOTIC EDEMA. The edema of cirrhosis, in the main ascites, has been relatively resistant to diuretic therapy and a specialized mechanism of edema formation has been suggested as a reason. On the other hand, sodium is retained with this form of edema and any device which produces a negative sodium balance will, therefore, induce some diuresis in the patient with cirrhosis.

While Ricketts *et al.*[295] find that mercurial diuretics are of little practical value in cirrhosis, Hilton[165] states that patients with cirrhosis who fail to re-

spond to the mercurial diuretics often exhibit satisfactory results if ammonium chloride is given along with it. He warns against hypopotassemia in patients so treated. Faloon *et al.*[94] report that salt-poor albumin in conjunction with the mercurial diuretics and low sodium diet usually increases sodium excretion in these patients. Patek *et al.*[268], on the other hand, report that such a diuresis in their patients was not sustained nor did it correspond with disappearance of ascites or improvement in hepatic function. Lowe and Overy[209] found that rigid restriction of sodium in the diet often resulted in protein sparing, reduced rate of ascites formation and, consequently, reduced need for abdominal tapping. Others have reported diuresis after the exchange resins[225,236,252,300,334], but opinion on their utility is mixed, and, as matters stand, none of our current therapies appear to be either potent or uniformly effective in this condition.

GLAUCOMA. Carbonic anhydrase facilitates the formation of intraocular fluid and, therefore, it is not surprising that carbonic anhydrase inhibition should have been tried for the relief of glaucoma. Becker[15,16] found that doses of acetazolamide (Diamox) of 0.5 to 1.0 gm. lowered intraocular pressure in glaucoma. Both oral and intravenous administration are effective but there is no report on local application. Grant and Trotter[134] confirming these observations also suggest the supplemental use of the miotic drugs. Breinin and Gortz[35] found that the effect on intraocular pressure was short-lived and that refractoriness soon developed. Their best results, which often were dramatic, were obtained in acute glaucoma while protracted therapy was apt to have uncertain results.

ANGINAL SYNDROME. The relief provided by mercurial diuretics to patients with the anginal syndrome, especially angina decubitus, was reported by Gold some years ago. Paul[269] confirmed these observations in 5 cases in which angina decubitus was successfully relieved with a mercurial diuretic. Foldes[107] more recently reports "A new therapy for angina pectoris" in which he relates the condition to disturbances in water metabolism and states that Mercuhydrin in combination with aminophylline, orally and rectally, provided relief for a "majority" of his patients. Further experience is necessary to establish criteria for the selection of suitable patients for this treatment. Until then, the only patients with anginal pain for whom this form of therapy can be prescribed with reasonable assurance of benefit are those with angina decubitus.

BROMIDE INTOXICATION. In 1941 Bodansky and Modell[30] indicated that the mercurial diuretics accelerated the excretion of the bromide ion. The successful application of this action to the treatment of bromide poisoning has been reported by Hussar and Holley[170].

MIGRAINE. Foldes[108] has recently reported on an "antiretentional therapy" for migraine in which he postulates cerebral edema and for which he suggests that diuretic therapy can be used for both prophylaxis and treatment. This concept is without confirmation.

EPILEPSY. Bergstrom *et al.*[23] and Merlis[241] report diminution of epileptic seizures with the use of acetazolamide (Diamox) but the former suggest that this action of drug is of limited value. No adequate explanation has yet been offered for this effect.

EDEMA OF PREGNANCY. Orloff *et al.*[266] report that salt-poor albumin produced diuresis with relief of edema in a patient with toxemia of pregnancy. Brown and Sutherland[39] report ammonium chloride produced increases in sodium excretion with relief of the edema of pregnancy. While mercurials were even

more effective, they suggest caution when they are used during pregnancy.

PREMENSTRUAL TENSION. The demonstration of premenstrual retention of salt and water has led to trial of natriuretic agents in tension states related to it. Morton[251] and Greenblatt[135] suggest that salt restriction as well as a variety of diuretics are useful in relieving the condition. It must be pointed out that it is difficult to distinguish between pharmacodynamic and psychologic aspects of relief in this condition and that what is lacking, and essential to establish diuresis as a useful therapeutic device for premenstrual tension, is a well-controlled double-blind test.

The Several Diuretics. The diuretics presently available are sufficiently potent for most purposes; new diuretics are sought for other reasons: 1) convenience in administration, 2) reduced toxicity, 3) effectiveness where others are ineffectual, 4) applicability in instances in which others are contraindicated.

SCREENING OF DIURETICS. The screening of diuretics for clinical utility is a matter of practical importance. Early enthusiasms often are not supported by subsequent trials in man. Such discrepancies may arise from the fact that the responses of animals differ from those in man but there is also the fact that final clinical evaluation is determined in the patient with congestive heart failure, a condition which can not be duplicated in the animal. Modell[249] assayed the same diuretics in the rat, the dog and in patients with congestive heart failure, and found that the results in the dog tended to resemble those in man much more closely than those in the rat. Clarke *et al.*[57] described the dosage-response curve of mercurial diuretics in the patient with congestive heart failure and suggested that it might be used as the basis of the comparison of the relative potency of these agents. Bioassay methods in man, of some precision, have been described by Ford *et al.*[109] and Greiner *et al.*[140,141,142,145]. Bioassay of diuretics in the patient with congestive heart failure, however, usually provides answers which apply much more to potency than to long-continued utility.

MERCURIAL DIURETICS. In a recent editorial[87], the mercurial diuretics were called "the greatest advance in the treatment of chronic congestive failure since Withering." There are suggestions that they may sometimes surpass digitalis in the relief of cardiac edema[147,312]. The relative importance of the two drugs, however, appears to vary with the particular situation[144,250].

Despite publication of an increasing number of reactions, the mercurial diuretics retain their position of preeminence[127] and, as a matter of fact, their use has increased through introduction of new forms and the extension of therapeutic usefulness to such important areas as the prophylaxis of pulmonary edema[128], asthma complicated by heart disease[129] and bromide poisoning[170].

Historical. The details of the discovery of such importance always excites interest. Although the diuretic action of mercury had been recognized since Paracelsus[288], the application of this action to the relief of edema is surprisingly modern. Only recently have the details of its modern discovery been revealed in publication by an on-the-spot observer[370].

The scene may be set briefly. The date, October 7, 1919; the place, Saxl's clinic in Vienna; the patient, Johann ———, a young girl with congenital syphilis; an all-important but still unidentified nurse; the informant, Alfred Vogl, then a third year medical student, now the author of the text, Diuretic Therapy[371]. On the historic day, Vogl had been ordered to administer mer-

cury salicylate to Johanna for her syphilis, but, because of some difficulty in obtaining that preparation, he injected a more readily available agent, a sample of a new organic mercurial, Novasurol, then being assessed for antiluetic potency. Since Novasurol soon proved to have no merit as an antiluetic agent, nothing noteworthy might have happened had not the nurse, entirely on her own, kept a striking graph of the patient's urine output. This, it appears, was the banner which brought the diuretic propensities of Novasurol to the attention of the medical staff, led to an organized study of this action and, eventually, to the publication in 1920 by Saxl and Helig which, unlike Vogl's more complete account, failed to give proper credit to the part played by the unidentified nurse.

Since that time, Novasurol has been replaced by other mercurials, less toxic but with no significant increase in diuretic potency. Some details of the actions and effects of the mercurial diuretics will be considered here, but, for fuller considerations of their clinical application and uses and for reference to older work, the reader is referred to publications by Batterman[10,11], Geiger[127], Pitts and Sartorius[282], Ray and Burch[288,289], and Vogl[371].

Mode of Action. The nature of the action which results in diuresis and the site of this action remain subjects of dispute and active investigation[282]. It is usually accepted that the water diuresis is secondary and obligatory to diuresis of salt but there is no agreement whether this be primarily natriuretic or chloruretic.

That chloride-containing salts, such as ammonium chloride, can potentiate the diuretic action of mercurials; that hypochloremic alkalosis is the more common form of electrolyte disturbance occurring after their excessive use; that when in hypochloremic states mercury fails to induce a diuresis, the addition of any chloride may restore its diuretic activity; are often taken to indicate that the mercurial inhibits the resorption of the chloride ion and that this leads to an obligatory sodium loss[125,126,240,317]. On the other hand, there are others[312] who hold that, since hyponatremia has been reported following the use of the mercury, a natriuretic action is primary and that the chloruresis and diuresis of water are obligatory. Other, more direct evidence for a primary natriuretic action is offered by Farah and Koda[97].

Evidence on the relationship of excreted electrolytes fails to clarify the problem[65,189,261]. Pitts and Sartorius[282] suggest that conclusive evidence for the answer to this basic problem of specific electrolyte inhibition may not be at hand.

Role of Mineral Corticoids. Farah[95] has described DOCA and ACTH pretreatment as failing to inhibit mercurial diuresis, whereas Axelrod[5] found that ACTH markedly reduced the diuretic response. Schemm and coworkers[48,158] have described instances of resistant cases of edema in which the use of ACTH and cortisone resulted in response to the mercurials. Should hormones play a role in the action of mercurial diuretics, the nature of such an action is not understood.

Enzyme Inhibition. Evidence has accumulated to support the view that the mercurial diuretics operate through a reversible but specific inhibition of enzymes essential to specific ion resorption in the renal tubule. In mercury intoxication, inhibition of sulfhydryl (SH)-containing enzymes has been demonstrated. That this effect, as well as the diuretic action, can be reversed by dimercaprol (BAL), which competes for mercury with SH-containing materials, is taken to indicate that mercurial diuretics exert their action

through the inhibition of such an enzyme[151].

Studies by Goth, Holman and O'Dell[133] indicate that mercury can inhibit ATPase activity in the homogenized rat kidney, but the bulk of investigation has been directed toward the action of mercurial diuretics to inhibit succinic dehydrogenase, one of the rather widely distributed SH-containing enzymes. Succinic dehydrogenase inhibition within the renal tubule has been demonstrated by histo-chemical means in the rat by many[45,46,258,259,294,307,361,376,377]. Handley and Lavik[152] demonstrated that BAL completely inhibits the action of mercury on succinic dehydrogenase in the dog kidney and that maximal recovery from this inhibitory action corresponds with the recovery from the diuretic effect of the drug.

Similar inhibition of succinic dehydrogenase can also be demonstrated to occur in other organs in which the mercurials exert no demonstrable pharmacodynamic effect. Ruskin and Ruskin[305] have demonstrated that Mercuhydrin suppresses dehydrogenase activity in the rat heart. Sexton and Russell[323] have demonstrated a similar action in the goldfish gill which appears to interfere with the transport of sodium in the gill against a diffusion gradient.

In different hands and with different mercurial diuretics, the apparent sites of this action vary somewhat although, in the main, it has been limited to some portion of the proximal tubule. Cafruny *et al.*[46] found that, in the rat kidney, there was a concentration of the enzyme in the brush borders of the proximal tubules which was greater than that in the cells of the proximal tubules, the distal tubules or collecting tubules, that inhibition by mercury was greater within the proximal tubules and the brush borders than in other sites in the renal tubule. Rennels and Ruskin[294] reported inhibition of succinic dehydrogenase limited almost entirely to the proximal tubule, that this paralleled diuresis and, in addition, could be prevented by the prior application of BAL. Mustakallio and Telkka[258,259] and Telkka and Mustakallio[361] found that while the succinic dehydrogenase was observed in the thicker or distal segment of Henle's loop, complete inhibition was not seen and that the main inhibition was found at different levels of the proximal tubule. Wachstein and Meisel[377] found inhibition by mercury was also restricted to the proximal tubule.

Despite this histochemical evidence of the effect of mercurials on succinic dehydrogenase, there is no direct evidence that this is the effect by which the organic mercurials induce their pharmacologically useful actions. Fawaz and Fawaz[100,101] point out that there is no proof whatever of the participation of succinic dehydrogenase in the process of the resorption of sodium, chloride or water in the renal tubule and make the categoric statement that, while it may be the case that mercurial diuresis involves the activity of an SH-containing enzyme, such an enzyme should be sought elsewhere than in the Krebs' cycle.

Site of Action. While it is usually accepted, on the basis of old and classic experiments, that the mercurial diuretics act directly on the renal tubule to decrease the rate of sodium chloride and water reabsorption, there is active dispute regarding the portion of the convoluted tubule in which this takes place.

Work on the distribution of mercury in the fluids and tissues of the body has not yet helped identify the site in the nephron of the action of the mercurial diuretics. Studies by Ray *et al.*[290] with radio-active mercury indi-

cate that mercury is not equally distributed through the body. While no measurable amounts of mercury were found in the cerebrospinal fluid, sweat, gastric juice and erythrocytes, and only a very little in saliva, peritoneal fluid and in edema fluid, it was high in bile and, of the tissues, in highest concentration in the kidney. Pitts and Borghgraef[280] also report the concentration of mercury in the kidney. Ray *et al.*[290], however, feel that there is no necessary correlation between the concentration of the mercury in the kidney and its renal action.

Proximal Tubule. The majority of opinion, based on a variety of methods of investigation, different animals and different forms of inferential thinking, leans toward the proximal tubule as the site of the diuretic action of the organic mercurial. Brodsky and Graubaith[37], using hydropenic dogs, Farah *et al.*[96,98,99] studying the effects of varying sodium loads and Gardier and Woodbury[125,126] following bicarbonate reabsorption which is assumed to occur in the proximal tubule as the site of action, all believe that their evidence points to the proximal tubule as the site of action. Weston *et al.*[389], inferring from the absence of effect of mercurials on ammonia formation in man, suggest the proximal tubule as a site of action, although they do not feel that the participation of the distal tubule has been ruled out.

Distal Tubule. Perhaps the most substantial support to the distal tubule as the site of the action of the mercurial diuretics comes from Pitts and coworkers[49,84,281]. Their inference is based on the assumption that mercury can induce complete blockade of reabsorption of salt at the site of its action and that, since the largest effective doses of the mercurial diuretics induce only about 20% blockade, the distal tubule, in which about 20% of filtered sodium is resorbed, is the more likely site of this action. It must be added, however, that Pitts and Sartorius[282] have also expressed the view that the evidence for neither case is conclusive.

Absorption. Earlier reports have indicated that the mercurial diuretics are well absorbed after intramuscular injection but that aminophylline accelerates absorption from muscle and decreases local irritant action and, therefore, makes an admixture desirable[282]. Earlier studies indicated that there was no significant difference between the diuresis induced by intramuscular and intravenous injection. Warshaw *et al.*[383] reported that Mercuhydrin was effective by the subcutaneous route. More recently it was shown that the oral administration of Mercuhydrin exerted only about 1/25th the diuretic effect of similar parenteral doses[224]. Overman, Gordon and Burch[267] found that there was such poor absorption of radioactive mercurial diuretic from the gastrointestinal tract as to preclude the usefulness of the oral route in the treatment of congestive heart failure.

Excretion. The rate of excretion of the mercurial diuretics has practical importance in relation to the frequency with which doses may be given with safety, especially in instances of diseased kidneys in which the possibility of cumulation as well as nephrotoxic action have been stressed.

Weston *et al.*[388] found that there was rapid binding of mercurial diuretics with protein so that the level of mercury in plasma falls sharply in the first 30 to 45 minutes after injection, which might be misconstrued as evidence of very rapid elimination. Recent studies on the excretion of labelled mercurial diuretics by Burch *et al.*[42] indicate that in the normal there is detectable mercury in the urine for about 24 hours and that congestive heart failure delays the rate of excretion, but the clinical

significance of this delay is not clear. Forney[110] found differences in the rate of excretion of mercaptomerin and merethoxylline, about 60% of the former and about 75% of the latter being excreted in 20 hours; in all cases, however, a large proportion within the first day. Grossman *et al.*[149] found no significant fecal excretion of the mercurial diuretics in man, while approximately 50% could be recovered from the urine in 2½ to 3 hours after injection and from 60 to 95% in 24 hours, and that the subcutaneous injection reduced this rate from only ½ to 1 hour. He also found that neither DCA nor ammonium chloride affected renal excretion of the mercurial diuretic but that aminophylline accelerated it in a single patient. Huffman[169] presents evidence that when mercurial diuretics are given by mouth they are more slowly excreted than when administered parenterally.

Toxic Reactions. The older literature contains many accounts of patients who received several hundreds of injections of mercurial diuretics with long-continued effectiveness and without special incident or renal injury. There are also patients who have reacted badly, some after the first dose of mercurial but, in most instances, after a period of salutary results. This is not surprising in view of the potency of the drugs as well as their wide-scale use. These have been thoroughly described in the literature[371] and the present account will consider only briefly such reactions which seem to add something to the already well-known picture.

Digitalis Reintoxication. There is the now almost classic view that when mercurial diuretics act to release large amounts of fluid locked in the tissue interspaces, there is also liberated such digitalis as may have been fixed in the fluid, and that in the already well-digitalized patient this supplement of digitalis may sometimes be sufficient to induce symptoms of digitalis intoxication. This view, however attractive, has never been supported by substantial evidence and it may well be assumed that the *coup de grâce* was delivered by St. George *et al.*[350]. These investigators, using micro-techniques, measured the digitoxin content in edema fluids of well-digitalized cardiac patients with congestive heart failure and noncardiac patients with ascites or pleural effusions. In half, no digitoxin was detected in the edema fluid, while in the remaining half the amount was so small (less than 20 micrograms per liter) that redigitalization is not conceivable.

Electrolyte Disturbances. These have attracted the greatest part of the recent attention devoted to reactions following the mercurials. It may be presumed that this is due to an increased interest in problems of electrolyte balance in general, as well as to the fact that the mercurial diuretics have been combined with stringent sodium restriction as well as with other devices for enhancing a negative sodium balance[54,168,176,258,316,343,351,379]. Jaffe, *et al.*[174] stress this danger in the elderly patient although it is not clear whether this is a problem of age or poor renal function. Holley and Hogan[168] list several varieties of electrolyte disturbance, hypochloremic alkalosis, hypopotassemic alkalosis, hyponatremia with hypervolemia and wih hypovolemia, which may be encountered. Emphasis has been placed on the importance of preventing electrolyte upheavals and the difficulty of reversing the process by replacement with an apparently appropriate parenteral fluid[379].

Lowe[210] has pointed out that there are cyclic phases in the clinical aspects of congestive heart failure, in spontaneous diuresis and in the diuresis induced by the mercurials. Such variations may account for variations in the

electrolyte responses and electrolyte disturbances in patients with heart failure who are treated with the mercurials.

Other Reactions. Brown[38] has reviewed the subject of reactions to mercurial diuretics and has grouped them into toxic and allergic reactions. In addition to the symptoms attributable to electrolyte disturbances, he lists chills, fever, malaise, muscular aching, nausea, erythema, chest pain, vomiting, dyspnea, tetany, and allergic reactions.

Marvel and Shullenberger[226] and Shane and Martin[325] report thromboembolic complications in patients with congestive heart failure following energetic diuresis with mercurials but neither have established the drug as the cause. Fineman and Rosenberg[105] report chills and fever with exfoliative dermatitis in one patient. Bender, Hoxsey and De Marsh[20] cite a case of neutropenia after a mercurial diuretic given for 10 months, with striking improvement following discontinuation of the mercury and administration of BAL. Silverman and Worthen[329] report a case of agranulocytosis in which mersalyl with theophyllin and Mercuhydrin each caused bone marrow depression while Thiomerin did not. Reeves[292] reports retrosternal pain with chills and fever after Mercuhydrin in a patient who did not have these symptoms after Thiomerin. Wohl, Shuman and Turner[396] report that mercurial diuretics significantly increase the rate of thiamin excretion in patients with congestive heart failure but there is no evidence that the thiamin loss may be such as to cause symptoms.

Prevention of Reactions. In view of these reactions, means of avoiding them is a matter of some interest. Caution against the excessive use of mercurials and, more specifically, against excessive diuresis, is general[381]. Modell[248] has shown that muscular cramps developing after the use of mercurial diuretics correlates better with the diuresis than with the dose of mercury injected.

Salt. Waldman and Pelner[379] suggest that in order to prevent electrolyte disturbances, patients receiving a mercurial diuretic should receive not less than 4 gm. of salt on that day. The question arises, however, whether this may not have a depressant action on the diuretics and whether the problem could be better solved by giving a smaller dose of the mercurial.

Skin Tests. Brown's[38] statement that skin tests are usually of little value in avoiding allergic reactions is supported by Harris[156].

Substitution of Other Diuretics. Some patients with a history of allergic reaction to one mercurial diuretic may tolerate another[292,329,386,394]. Such substitutions are not invariably safe in cases in which the history is one of a severe reaction; the safest recourse is to a nonmercurial diuretic.

Specific Antidotes. A few specific methods of combating toxicity of mercurials have been suggested. While dimercaprol (BAL) has been shown clearly to reduce the acute toxicity[197], there is no good evidence that this also applies to the later toxic effects in which the amounts of mercury in the tissues may be minute. Older suggestions such as that by Pines of magnesium sulfate to prevent ventricular fibrillation have been reported as useless by Craver *et al.*[63]. The suggestion that ascorbic acid might provide a useful antidote[324] has not been substantiated by clinical trials[141].

Cohn[58] reports that some symptoms of hypersensitivity can be prevented by the concomitant use of antihistamine drugs. Wachstein and Meisel[375] found glycine and arginine effective in protecting rats against the nephrotoxic action of mercurials. Their experiments, however, were conducted with doses

of the organic mercurials that produced effects on the renal tubules more typical of the toxic action of ionized mercurials than of therapeutic doses of organic mercurials and, therefore, may have little application in the situation encountered in man.

Mode of Administration. The matter of the greater danger of the intravenous over the intramuscular injection has also been the subject of some consideration. It seems to be a fact that the rarely reported immediate death has become even more rare since the intramuscular injection has largely replaced the intravenous injection. Vogl[371] states categorically that there have been no deaths from the former. On the other hand, Wallner and Herman[381] make the reasonable statement that the intramuscular route is not a complete safeguard against serious systemic reactions.

Mercury Resistance. Rarely is mercury resistance encountered at the outset of the use of the organic mercurials and complete refractoriness may be considered outside the range of normal variability. Depressed responsiveness to the organic mercurials may, however, develop after a longer or shorter period of satisfactory reactivity. More often than otherwise this develops in urgently ill patients.

A variety of circumstances have been examined and suggested as an explanation for this state. Axelrod and Pitts[6] have shown in the dog that anoxia reduces or abolishes diuresis induced by mercury. Weston and coworkers[390] have suggested that resistance is due to a complex of factors promoting salt retention of which one may be increased adrenal cortical activity. Handley *et al.*[153] suggest decreased glomerular filtration rate as the cause.

Elkinton, Squires and Bluemle[90] state that their observations in patients refractory to mercury indicate that only in half of those with hyponatremia does the hyponatermia play a role, since only in about half did the administration of salt re-establish diuresis from the mercury. Farah and Koda[96] found that mercury diuresis was related to the concentration of sodium in the blood and that when plasma sodium was reduced, dogs became resistant to mersalyl. Schwartz and Wallace[317] found that sometimes, but not invariably, ammonium chloride will restore responsiveness which continues till hypochloremia again develops. Potentiation of the diuretic action of the mercurials by ammonium chloride has long been known and has been recently reinvestigated and corroborated[143,164]. Koza *et al.*[189] attacked this problem and state that as yet there is no entirely satisfactory explanation for the potentiation of the diuretic action of the mercurials by ammonium chloride.

The unconfirmed report of Vogl and Esserman[372] that aminophylline is an effective agent in this difficult situation is discussed in another section. In a recent paper, Waldman and Pelner[380] report that pyridoxine may be used to overcome mercury-fastness, but they provide no adequate explanation for the phenomenon nor is there any confirmation of it.

Self Administration. Self administration of diuretics is economically desirable for the patient and also makes possible daily instead of less frequent balancing of water and salt metabolism.

Subcutaneous Administration. There are reports of the satisfactory self administration of mercaptomerin (Thiomerin) by Bower[32] and Krehbiel and Stewart[191] while Sussman and Stein[357] and Warshaw *et al.*[383] have reported, on a large scale, satisfactory subcutaneous administration of Mercuhydrin.

Rectal Administration. Salyrgan (mersalyl) and Mercuzanthin (mercuro-

phylline) had been administered in suppository form in previous years but discontinued largely because of a high incidence of proctitis, not because of lack of effectiveness. Levokove and Sarrow[203] have reported satisfactory results with meralluride (Mercuhydrin) suppositories without rectal or colonic reactions. The absence of additional favorable reports in the 5 years since this paper was published may, however, be taken to imply limited utility.

Oral Administration. Since this mode of administration is so desirable, the search for more tolerable oral mercurial diuretics is a very active one[76].

Salyrgan and Mercuzanthin have been known to be effective orally but the high incidence of gastrointestinal intolerance limited their use. Vander Veer *et al.*[368] reported that Mercuzanthin administered orally to 27 patients removed or reduced the need for parenteral injections. The duration of treatment possible with continuing favorable results is not, however, indicated. Mercuhydrin has been reported as effective and tolerable by the oral route by Shaffer *et al.*[324], whose patients took medication for 3 months. However, it may be noted that 25% exhibited some manifestation of toxicity, salivation, nausea, vomiting or bloody diarrhea. The authors suggest that ascorbic acid, which does not decrease diuretic effectiveness, overcomes undesirable reactions. Greiner and Gold[141] found that the addition of ascorbic acid to Neohydrin (chlormerodrin) did not significantly reduce the incidence of gastrointestinal distress after oral administration.

Neohydrin. Chlormerodrin (Neohydrin) is, at the time of this writing, the most widely used oral mercurial diuretic[81,82,132,194,196,229,255,256,257,330,338]. Moyer *et al.*[256] report only 5 to 10% absorption, hence 10 times the parenteral dose is required when given orally. Greiner *et al.*[141] report that, while Mercuhydrin is 1/24th as effective orally as parenterally, the ratio is reduced to 1:6 when Neohydrin is used, and that when given by mouth, dose for dose, Neohydrin is 4 times as effective as Mercuhydrin. Bradford[34] reports good results as well as economic advantages in 80% of his patients. Lawrence *et al.*[194] report that in 70 patients with congestive heart failure 97% did as well or better with Neohydrin than with parenteral doses of Mercuhydrin. It should be pointed out that 35% of these patients also did well on placebo alone. Leff and Nussbaum[196] found about a 12% incidence of unpleasant effects while the Neohydrin was used from 2 to 12 months. Snyder *et al.*[338] report that Neohydrin was effective in the control of congestive heart failure only when daily doses containing more than 60 mg. of metallic mercury were used, Goldman and Steigmann[132], while reporting good to fair results in half of a group of 48 patients, found the Neohydrin induced nausea in about one-fifth of the group.

Although very rare after the administration of the mercurial diuretics by any route, a case of mercurialism due to the oral ingestion of Neohydrin, is reported by Cáceres and Stauffer[44]. In this case, there were sore gums, a blue-black gum line and a rise of the blood nonprotein nitrogen level. That improvement followed 2 days after cessation of the Neohydrin is taken to support the case for true mercurialism.

Others. Pollock and Pruitt[284] suggest mercumantilin (Cumertilin) as an effective and satisfactory oral diuretic. Stroud *et al.*[354] report that Mercurital was effective orally, but that, like other oral diuretics, soreness of gums, cramps and diarrhea occurred. Merpurate is reported by Kaufman *et al.*[184] to be effective, able to replace parenteral therapy completely in patients, but no

statement is made indicating the extent of congestive failure in their patients or the duration of such successful treatment.

Summary. Whereas virtually all organic mercurials exert diuretic action when administered by mouth, there are sharp limitations to this convenient route of administration due mainly to a higher incidence of distressing symptoms, especially the gastrointestinal. In this connection it is well to recall that most bioassays of the diuretic potency of the oral diuretics in man fail to take into account undesirable effects in the gastrointestinal tract which develop only after the long continued use of the drugs.

NEW MERCURIAL DIURETICS. *Mercaptomerin (Thiomerin) and Other Mercaptomercurials.* The detoxifying action of thiols of mercurial diuretics has been known for some time[151,197,198,327]. The dithiol, BAL, is completely antagonistic to the action of mercury and no diuresis results when they are given simultaneously. The introduction of a monothiol group into an organic mercurial, however, seems not to interfere significantly with diuretic potency of mercurial diuretics, such as mercaptomerin (Thiomerin), while it reduces acute cardiac toxicity and local irritant action[197,198,306]. Satisfactory clinical results with Thiomerin in the treatment of congestive heart failure have been reported by many[93,148,349,367,395].

Capps *et al.*[50] agree with others that acute toxicity is indeed reduced and local irritation is eliminated but that, in the rat, in terms of chronic effects, Thiomerin is more toxic than Mercuhydrin or Mercuzanthin. Ruskin and coworkers'[307] work on rats indicates that inhibition of renal respiration by Thiomerin is the same as with other mercurials and that there is no diminution of nephrotoxic action. Barrett[9] and Handley *et al.*[153] have evidence that, in the dog, Thiomerin has a higher renal toxicity than other mercurial diuretics.

There are also clinical reports that Thiomerin is not without disadvantages in man. Winik and Benedict[395] report subcutaneous infiltration of long duration. Gold *et al.*[131] experienced systemic reactions as well as a high incidence of local reactions after Thiomerin and they point out that thiol-containing compounds are known to be of relatively high allergenicity. Weissman and Gelfand[385] cite the case of a patient who could tolerate Mercuhydrin but who, following Thiomerin had fever, cramps, pruritus, rash and circulatory collapse.

Frisk *et al.*[119] report that another mercapto-mercurial, Diurgen, induced only 2 cases of serious toxicity of 274 cases, as compared with 4 times that number with Mercuhydrin. It may be stated that the latter figure is considerably higher than that usually reported and that, therefore, these results cannot be accepted without reservation.

Handley *et al.*[154] and Moyer *et al.*[253] have reported on an oral thiol-containing diuretic which, they found exhibited little toxicity but was too little effective to be useful, while Dimitroff *et al.*[76] reported this compound both ineffective and relatively toxic.

Others. Merethoxylline (Dicurin) has recently been introduced. It is usually sold in a mixture containing procaine. The drug appears to be about as effective as most of the mercurial diuretics now on the market but statements of decreased local irritant action have not yet been confirmed[26,53,297].

Mercumantilin (Cumertilin) has been reported to be about as effective by parenteral injection as others in common use[326,328]. Batterman and his coworkers[12,299] report that Cumertilin neither responds to ammonium chloride nor requires it. They also report that

the drug is effective when administered by all common routes. Mergamate is reported by Simon *et al.*[331] to be effective and satisfactory by subcutaneous injection. Confirmation is awaited.

Handley *et al.*[155] report that three mercurial derivatives of 2-methoxypropylurea were given to dogs over prolonged periods without changes in glomerular filtration rate, blood pressure or formed elements of the blood, but without trial in man. White and Nuhfer[393] report on 3 allylurea mercurials with diuretic effects of the same order as Mercuhydrin but information on clinical trial is not available.

EXCHANGE RESINS. Although long used in industry, the application of the principle of ion-exchange to the treatment of edema is relatively recent. Dock is generally credited with the introduction into medicine, about 8 years ago, of resins which removed the sodium ion from the contents of the bowel and thereby provided not only a method of de-salting palatable food after it had been eaten and relished but, if enough sodium was removed, a diuretic action as well. The attractiveness of the concept, the early reports of minimal toxicity and the desire for a substitute for the salt-poor diet led to widespread trial with extensive use of several types of ion-exchange resins. Extensive reviews of this subject are available and for greater detail the reader is referred to those by Arnold[4], Danowski *et al.*[70,71], Dock and Frank[79], the Cornell Conference on Therapy[60], the symposium on the subject edited by Miner[247], and for chemical and technical details to the paper by Bauman and Eichhorn[14].

Mode of Action. The ion-exchanger used in medicine is usually a resin of a sandy or gritty nature, although it may be a fine powder. While it is relatively inert chemically, it has the capacity for exchanging one of its ions for others of similar charge, which ions in particular depending on the resin, the ions available and the nature of the medium. After the exchange, the resin remains relatively inert and is not absorbed so that, provided proper circumstances prevail while the resin is being excreted, it will have removed particular ions from the intestine and substituted others for them. To the extent that this exchange induces a negative sodium balance, edema is freed and diuresis ensues. The amount of a particular ion which may be removed by an exchanger may be calculated on a stoikiometric basis, but many factors may prevent the reaction from proceeding to theoretic completion. As the amount of sodium available for exchange falls, the potential of the exchanger for its removal also falls. The presence of other ions interferes with sodium exchange. Ions with high valence tend to displace those below it. Calcium in the gastrointestinal tract, for example, tends to limit sodium exchange. Atoms of higher atomic weight tend to displace those below them, hence potassium also interferes with sodium exchange. The pH of the media also influences the rate and extent of exchange, varying with different types of exchangers.

In any event, the situation in the bowel rarely provides ideal conditions for sodium exchange. Whereas a gram of a particular resin may have the theoretic capacity for removing 10 mEq. of sodium, even under the most favorable circumstances provided by the normal bowel for exchange, only about 3.5 mEq. are likely to be removed. When the sodium in the diet is restricted, the gram of resin may remove less than 1 mEq. This makes necessary the use of very large amounts of resin for the removal of practical amounts of sodium.

Elkinton *et al.*[89] found that, in patients with colostomy, fecal excretion

did not greatly exceed dietary intake of sodium, suggesting that the final action of the resins develops in the lower bowel, a view with which McChesney is in agreement[232]. Bernstein and Evans[24] suggest that hormonal factors may also be involved in regulating the exchange.

Types of Resins. Although there are, of course, both anion and cation exchangers, only those which remove sodium induce diuresis. The sulfonic acid and the carboxylic acid cation exchangers are the forms in common clinical use. The first is the more strongly acid and the more rapid exchanger. Although the carboxylic resins have a greater capacity for exchange, in the medium existing in the gastrointestinal tract, the sulfonic resins tend to remove more sodium. There is no preponderant opinion regarding the preferability of either the sulfonic or the carboxylic resin[70,136,137,138,139,162,178,188,233,234,236,277]. Combinations of carboxylic and sulfonic resins have not proved particularly advantageous either.

The nonspecific character of the exchange process results in the removal of other ions as well as sodium and to compensate for this, resins which release other ions may be added to the hydrogen releaser. Such combinations, unfortunately, still further decrease the sodium-removal capacity of the exchangers. Studies by McChesney[231] indicate that exchangers which contain between 1 and 2 mEq. potassium per gm. provide adequate protection against hypopotassemia in the average case, but a diet containing less than 1 gm. of salt diminishes this protection appreciably. Depletion of calcium and magnesium is also possible but usually their loss is minimal and no addition of these minerals is ordinarily made to exchangers. Dock and Frank[79] emphasize that there is, nevertheless, a distinct risk of gradual demineralization of bone in patients on a steady diet of exchangers over a period of years and mention two cases of tetany.

In exchanging the H-ion for sodium, the danger of acidosis is a real one. This can be compensated for to a degree by admixture to the resin of potassium which, if excessive, provides a possibility of hyperpotassemia. Elkinton *et al.*[89] found the ammonium resin removed more sodium than the potassium resin. Unfortunately the ammonium resins provide no protection against acidosis. Glycine exchangers have been made which are effective but are disagreeable to take, often causing nausea as well as acidosis. Lithium exchangers present the dangers inherent to lithium.

The most acceptable resins are mixtures of ammonium or hydrogen exchangers or the potassium exchangers in a 2 to 1 or 3 to 1 ratio. Whereas Greenman *et al.*[138] suggest a use for mixtures of anion and cation exchange resins in special instances, such as renal disease, Martz *et al.*[225] find them contraindicated in that condition.

Effects on Electrolyte Balance. The fundamental action of the resin, to exchange one ion for another, is, unfortunately, not highly selective and ions they remove as well as those they provide in exchange may cause disturbances of electrolyte homeostasis, some of which may be beyond the capacity of the compensatory mechanisms of of the body[31,67,68,69,72,85,89,92,103,115,136,138,139,157,187,190,202,233,234,335,391].

Others discount the importance of such possibilities, Emerson *et al.*[91], pointing out that adaptive reactions of the intestinal tract prevent the depletion of sodium by the resins, stating that there is no evidence of depletion of sodium stores through the continued use of the resins, that the fecal sodium excretion continues to diminish with

the continued use of resins. Coincidentally with this, however, there is a tendency for fecal potassium to increase and in patients receiving the resins for prolonged periods for the potassium removed to exceed that of the sodium. Schwartz and Relman[315] found that hyperchloremic acidosis from resins was rarely severe. Greenman *et al.*[139] feel that after 6 months use there may be danger of hyponatremia and hypocalcemia. Weston *et al.*[391] and Levitt[202] report negative sodium balance in patients on low sodium diet and a tendency to hyperchloremic acidosis which was greater in patients with renal disease. Danowski and Greenman[67] found that liberalization of the diet was not possible if the resins were to be effective and that prolonged therapy might well lead to potassium deficit and acidosis. Friedman[115] lists as disturbances which may develop, acidosis with hypochloremia, hypopotassemia, hypocalcemia, and elevated blood urea nitrogen levels.

Clinical Experiences. Congestive Failure. Satisfactory results in the treatment of patients with congestive heart failure have been reported by a large number of observers[1,4,24,47,64,102,157,186,273,373,374,398], who, in general, feel that, while the resins provide advantages as an adjunct to more potent diuretic therapy, they also have practical limitations. Bonner[31] states that most of his patients preferred the low-sodium diet to resin therapy. Nor do the resins eliminate the need for sodium restriction, for such large amounts of resin are needed to remove practical amounts of salt from the normal diet as to make bulk a serious problem in the matters of ingestion, elimination and local irritant action. Field *et al.*[103] call them a disappointment, finding that both colon and kidney tend to conserve sodium more than potassium and that when salt is restricted the resins not only remove too little sodium to make them useful, but the hazard of potassium loss is also increased. Kraus[190] states that the affinity of resins for ions other than sodium is such as not to commend them and, in addition, he points out a danger of digitalis intoxication if hypocalcemia should develop.

Adjunct to Mercurial Diuretics. There are several reports[25,116,335] that the resins may enhance the action of mercury in cases otherwise relatively resistant or refractory to its diuretic action, or reduce the number of injections needed. Elkinton *et al.*[89] reported that resin appeared to potentiate the renal action of simultaneously administered mercury.

Edema of Nephrosis. The utility of resins in the nephrotic syndrome is discussed in some detail in a separate section above.

Cirrhosis. Effective use in cirrhotic ascites has been reported by many observers and is discussed in a separate section above.

Miscellaneous. Penman[274] found that resins were useful to mobilize excessive amniotic fluid, although they had no influence on the pre-eclamptic state. Arnold[4] and Danowski and Greenman[67] point out the usefulness of the simple hydrogen cation-exchanger in the treatment of hyperpotassemia. Emerson *et al.*[91] list the following additional situations in which cation exchange resins of one form or another may, presumably through the mobilization of sodium, also prove of value; obesity, premenstrual edema, edema of pregnancy. Groff[146] states that he has used exchange resins with some success in hypertension, although other equally satisfactory reports have not been published.

Untoward Effects. These may be listed as nausea and vomiting, gastrointestinal disturbances, increase in digitalis toxicity, generalized weakness,

constipation, in addition to the electrolyte disturbances already noted. Gastrointestinal complaints are common. Many warn against the use of these agents in renal disease, presumably because of the increased danger of acidosis. Peel and Semple[273] adjure the use of ammonium chloride coincidentally, presumably because the resins may, themselves, induce acidosis and hyperchloremia.

Friedman[115] found casts in the urine of patients without renal insufficiency. Kahn and Emerson[178] report that after resins, urinary ammonium failed to rise in 3 patients with severe renal damage and, as a consequence, acidosis developed. They use this experience as a basis for contraindicating the resins in cases with renal disease of any severity.

Highly specialized toxic effects have also been reported. Gabuzda *et al.*[120] reported that after ammonium resins neurological symptoms developed; drowsiness, apathy, weakness, slurring of speech, disorientation and tremor developed in 6 of 12 patients with cirrhosis, and concluded that patients with severe hepatic disease tolerate the resins poorly. Small and Maurizi[334] describe an alcoholic patient with cirrhosis in whom, after an ammonium resin, a psychotic episode developed which they presumed to be due to the resin. Friedman *et al.*[118] found that exchange resins inhibited the antibiotic activity of dihydrostreptomycin, Terramycin and Aureomycin, but not that of penicillin or chloramphenicol.

Summary. The theoretic advantages of the cation exchange resins are often overbalanced by realistic disadvantages, such as impotence, necessitating large doses for significant effects, unpleasant texture, making ingestion of these large amounts difficult, and irritant action leading to gastrointestinal difficulties[162]. The addition of potassium, while it provides protection against hypopotassemia, considerably decreases the effectiveness of the resin. The ability of the resin to remove sodium from the intestinal tract is also limited by a low-salt diet, yet the latter cannot be avoided because exchangers can rarely be taken in large enough amounts to produce a useful effect with average salt ingestion.

ACETAZOLAMIDE (DIAMOX). Mann and Keilin[217] reported in 1940 that the alkaline urine, containing increased amounts of sodium, produced by sulfanilamide, was due to inhibition of carbonic anhydrase. Mason[227] in 1947 pointed out the importance of gaseous exchange in water mobilization through the development of both acidosis and alkaline urine, and soon thereafter Schwartz[314] reported that sulfanilamide produced a small diuresis in patients. The preparation of drugs related to sulfanilamide, especially heterocyclic congeners, has been extensively reviewed by Roblin and his coworkers[246, 298], who are responsible for the preparation of many carbonic anhydrase inhibitors, including Diamox (acetazolamide).

There are many drugs which are known to inhibit the activity of carbonic anhydrase and to induce a diuresis. Dirnate (p-sulfonamido-benzoic acid) was reported by Lindsay and Brown[205] and Merrill[244] to be too feeble to be of real value. Only acetazolamide appears to be a practical diuretic but at the time of this writing other carbonic anhydrase inhibitors are under active investigation.

Pharmacologic Considerations. Maren and his colleagues[218,219,220,221,222,223] are responsible for a body of fundamental pharmacologic information. Carbonic anhydrase activity is reversibly inhibited by Diamox. This action decreases the rate of hydration of carbonic dioxide but by no means completely suppresses it. As a result, less H-ion is

available for the replacement of sodium in the phosphate buffer system of the urine and, therefore, more sodium and bicarbonate are excreted in the urine and more chloride is retained[83]. With the loss of sodium, there is an obligatory loss of water. Schwartz *et al.*[318] suggest that this action develops in the proximal portion of the renal tubule. Ruskin[304] has demonstrated that hemodynamic effects are not concerned in Diamox diuresis and also that the inhibitor exerts no depressant action on succinic dehydrogenase or adenosine triphosphate in heart and kidney.

The extent to which carbonic anhydrase inhibition develops depends on the dose and the concentration of Diamox. Maren and Wadsworth[220,221] have shown that when Diamox is given round-the-clock or in large single daily doses, alkalinization of the urine and diuresis ceases after 4 or 5 days. Leaf, Schwartz and Relman[195] found this effect began to develop in 2 days. They conclude that the self-limiting action of Diamox is not due to a cessation of the inhibitory action on the carbonic anhydrase but to lowered filtered bicarbonate because of lowered blood bicarbonate levels. Maren and Wadsworth[221] explain the self-limiting action as a consequence of metabolic changes because of which carbonic anhydrase is no longer the rate-controlling factor in H-ion excretion.

The effectiveness of Diamox returns 2 or 3 days after it has been discontinued and appropriate readjustments of electrolyte have taken place. Because of this, the drug is now usually given in an interrupted regimen: 3 or 4 days of treatment alternating with a similar period without the drug.

Diamox is well and rapidly absorbed from the gastrointestinal tract reaching a peak of action within 2 hours. About 70 to 90% is excreted unchanged in the urine within 24 hours. The effect of a single dose may last from 6 to 12 hours. The single ceiling dose has been established to be of the order of 500 mg.[51]. Doses smaller than 250 mg. are not likely to be effective by mouth although they may be so when given intravenously.

The action of carbonic anhydrase is not restricted to the renal tubule; it is an ubiquitous enzyme whose functions in all the tissues in which it is found are not understood. No organ or tissue has been shown to have a special affinity for the inhibitor and effects of Diamox exerted elsewhere than in the kidney are now being studied. The utility of Diamox in glaucoma through decrease in intraocular fluid formation, and in epilepsy through an ill-understood mechanism are discussed in another section. Studies in the dog by Birnbaum and Hollander[28] have shown that Diamox inhibits pancreatic secretion. Tschirgi *et al.*[364] cite experiments in cats and rabbits which indicate that Diamox causes as much as a threefold decrease in the rate of cerebrospinal fluid formation with a consequent fall in cerebrospinal pressure. Applications of this fact to man have not yet been established. Carbonic anhydrase present in red blood cells is inhibited by Diamox but this action has not yet been shown to be of any practical importance. Niedermeier *et al.*[264] have shown that, after Diamox, the sodium, bicarbonate content and buffering capacity of saliva falls, and that these changes are similar to those found when ammonium chloride is used in doses which cause an acidosis.

Effects on Electrolyte Balance. The development of Diamox action is followed by a rise in urinary pH, with increased excretion of bicarbonate, sodium, potassium and a decrease in chloride and ammonia excretion and titratable acidity. There appears to be little change in phosphate excretion. In

consequence of these electrolyte alterations, a hyperchloremic acidosis tends to develop.

Schwartz and Relman[315] reported that Diamox is not likely to cause serious acidosis because its self-limiting action restrains the development of the hyperchloremia and the acidosis. Israels *et al.*[175] report a self-limiting acidosis to occur in infants.

Clinical Experiences. Friedberg *et al.*[114] are generally given the credit for the first controlled clinical trial of Diamox. They reported a satisfactory experience in 23 of 26 patients with congestive heart failure, comparing favorably with mercurial diuretics administered parenterally. Other reports are equally favorable[19,200,304]. On the other hand, Relman *et al.*[293] were "disappointed" because half of their patients failed to lose edema. It is now generally conceded that Diamox is not as potent as the mercurial diuretics. It has assumed a position of practical importance, however, as an oral diuretic and as an adjunct to the mercurial diuretics.

Pulmonary Disease. Nadell[261] suggested Diamox for the treatment of congestive failure in patients with respiratory acidosis due to pulmonary disease. In chronic emphysema, defective ventilation may result in increased retention of carbon dioxide and the development of a chronic respiratory acidosis. To compensate for this threat to homeostasis, there is increased excretion of chloride ion and retention of bicarbonate. In this respiratory acidosis there are, therefore, high blood levels of both carbon dioxide and bicarbonate[356]. Consideration of the mechanism of the respiratory acidosis may suggest that Diamox could be harmful to such patients, since the effect of the Diamox is to increase bicarbonate excretion, hence to antagonize a compensatory mechanism. Although this is what actually happens, Schwartz *et al.*[319] found that, in patients with respiratory acidosis, there was nevertheless, a large diuretic response to Diamox as well as symptomatic improvement. They postulated that patients with cor pulmonale have an increased rate of tubular reabsorption of bicarbonate which may be mediated through increased carbonic anhydrase activity. If this were the case, there would be a particularly large diuresis after Diamox in such patients. Satisfactory results have also been reported in this condition by others[18,106,121,122,123,160,261].

Refractory Edema. Maren[219] reported that when Diamox was given for 24 hours preceding a mercurial diuretic, the total effect was greater than the effects of both separately. He concludes that the metabolic acidosis due to Diamox potentiates the natriuretic and chloruretic actions of mercurial diuretics in dogs. Investigation along these lines in man[303] indicate that Diamox together with ammonium chloride, given in doses sufficient to produce a hyperchloremic acidosis, alters the setting for the action of mercurial diuresis in such a way that patients previously refractory to them may respond with a satisfactory diuresis. Whether it is the acidosis or the hyperchloremia which contributes to this effect is not established.

Use in glaucoma and epilepsy is considered in another section.

Toxic Reactions. The earliest reports[114] contained accounts of paresthesias and drowsiness. These usually disappeared though the drug was continued. Serious toxic reactions have, thus far, been relatively rare. Kaye[185] studied the effects of single doses of 10 mg. per kg. given to normal controls and patients with renal disease. Such doses produced much the same effect on electrolyte excretion in normals and those with renal disease without acidosis. In subjects with renal disease

and acidosis, the Diamox was without much effect at all. In no instance did the single dose produce an untoward effect which was reflected in the urine, the blood pressure or blood urea nitrogen content.

The close chemical relationship of acetazolamide and the sulfonamide drugs suggest the possibility of related toxic reactions. One case of agranulocytosis following Diamox has already been reported by Pearson *et al.*[271].*

XANTHINES. Although drugs of this large group have long been known to exhibit diuretic activity and are still widely used for this purpose[348], their position in the therapy of edema is definitely secondary to that of the mercurials which are much more potent[145].

Pharmacologic Considerations. There is still some question regarding the mode of their action. An effect directly on the kidney seems to be established although there is the opinion that these drugs may also act to increase renal blood flow and glomerular filtration rate[282,336]. Neither the site nor the precise mechanism of the suppression of salt reabsorption in the renal tubule has been established.

Special merits, in addition to their diuretic action, have been attached by some to the xanthines in the treatment of congestive heart failure. Steinberg *et al.*[348] point to a fall in venous pressure and shortening of circulation time which they presume is due to peripheral dilatation, but this is not supported by proof. Investigations on the effect of aminophylline on the cerebral circulation by Wechsler *et al.*[385] have indicated that in man therapeutic doses may cause constriction of the cerebral vessels and a degree of cerebral anoxia. Moyer *et al.*[254] also found evidence of increased cerebral vascular resistance. Vogl and Esserman[372] recommend aminophylline as a supplement to mercury diuretics in "intractable" congestive heart failure. A study by Greiner *et al.*[145], in which the combination was subjected to precise measurements, did not support a contention of potentiation of the mercurials by the xanthines.

Administration. Truitt *et al.*[363] studied and compared the diuretic action of theophylline and the blood levels achieved after administration by oral, rectal and intravenous administration. They concluded that, all factors taken into consideration, the rectal retention enema was the optimal mode of administration while the rectal suppository was followed by too slow absorption to be useful. Waxler and Schack[384] found wide variations after the oral administration of tablets and suppositories with more consistently maintained blood levels after intravenous and intramuscular injection. Others[145] have also found the oral route less effective than the parenteral. The intravenous administration has been followed by fatality in a few instances[36].

Newer Xanthine Diuretics. Recently choline theophyllinate (Choledyl) has been suggested for the treatment of congestive heart failure as well as for the anginal syndrome, with claims for negligible gastrointestinal irritation[13]. The study in question has been the subject of a polemic in the columns of the Journal of the American Medical Association. Pearson[272] reported this compound was only a feeble diuretic. Another theophylline compound, the iso-propanilamine, was shown to be effective as a diuretic but not to exhibit special advantages[111]. Pamabrom, a bromotheophylline, caused appreciable distress and seemed to be of little value[80]. Silverthorne and Moyer[330] re-

*In the Jan. 21, 1956, issue of the J. Am. Med. Assn. (*160*: pp. 204 and 206) there are reports of renal lesions after Diamox similar to those after sulfonamides and of a case of thrombocytopenia.

ported that Parephyllin, a substituted theophylline derivative, had little to commend it over others, more commonly used, while it had many disadvantages.

Summary. The reasons for the secondary position of the xanthine drugs as diuretics may be briefly listed: 1) they are not as effective as the mercurials, 2) they are not as dependable as the mercurials, 3) given by mouth, the route of choice, effective doses cause a high incidence of gastrointestinal distress, nor is this effect appreciably decreased when similar doses are given by suppository, 4) given intravenously, fatalities may occur.

These do not, however, vitiate the uses dependent on the other pharmacodynamic action which they possess.

AMMONIUM CHLORIDE. Ammonium chloride has been used for its diuretic action as well as for its enhancement of the action of the mercurial and xanthine diuretics. Sartorius *et al.*[308], Rector *et al.*[291] and Wood[397] have explained the limited nature of ammonium chloride effects. At first it causes increased sodium excretion and diuresis. With continued ammonium chloride ingestion the renal tubule responds to the threat of excessive loss of the body's stores of base with increased ammonia formation. Within a few days this compensatory mechanism achieves equilibrium and the ammonium chloride becomes ineffectual. Schwartz and Relman[315] feel that ammonium chloride is of very limited value, stating that it causes little or no increase in sodium excretion, more potassium loss, hence is of little value in congestive heart failure and useful only for replacement of chloride. Wood[397] also reports that potassium is lost after ammonium chloride but in view of the relatively prompt adaptive response of ammonia production, feels this is not an important hazard.

Despite the protective device to conserve base, ammonium chloride may induce acidosis and such reports are to be found in the recent literature[260, 333,397]. Karr and Hendricks[179], reporting on the toxicity of intravenous ammonium compounds, attribute toxicity to the ammonium ion as well.

The enhancement of the action of the mercurial diuretics by ammonium chloride was estimated, in older studies, to average about 20%, with wide individual variations, and constitutes the major use of ammonium chloride in the therapy of edema. This has been variously attributed to the effect of relative acidosis and the influence of the chloride ion. Recently it has been shown that 9 gm. of ammonium chloride given for 2 days may double the effect of Mercuhydrin in some cases[143]. This synergism was of more practical value with smaller doses of mercurial than with 2 ml. doses. Hilton[164] concludes that this effect of ammonium chloride is independent of pH, bicarbonate or chloride concentration of the plasma and suggests that the ammonium chloride may induce some alteration in cellular metabolism. Batterman[12] states that these effects of ammonium chloride, for some unexplained reason, do not apply to a particular mercurial, Cumertilin (mercumantilin).

WATER. In 1942, Schemm revived the long-established principle that water alone may be used as the basis of the systematic treatment of edema. More recently he reviewed this form of treatment[309,310] and emphasized its importance, especially in patients with kidney disease.

The mechanism of water diuresis has been studied in considerable detail by Verney[369] who cites emotional, hormonal, physical and chemical factors. Water diuresis is not a self-limiting process, it may develop far more extensively than is generally appreciated,

sometimes causing severe dehydration. Large amounts (6 to 10 liters daily) are required, however, to induce a diuresis; small amounts of water may not only be ineffectual but may actually make matters worse[282]. Salt deprivation does not inhibit water diuresis[55,302]. Duncan[86] has shown that in the patient with congestive heart failure water may cause hyponatremia.

Rosenbaum *et al.*[301,302] have shown in normal subjects that water diuresis is affected by position, being inhibited by sitting and enhanced by reclining. Birchard and Strauss[27] state, however, that whereas in normal seated subjects saline will not induce a diuresis, it may do so in those already exhibiting a water diuresis. Thus the danger of tissue desiccation which attends excessive water drinking appears to be limited when saline is used.

The case for water as a clinical diuretic reposes on what may well be called the demonstration of a feat by Schemm, namely, that edema can be removed, if exceedingly large amounts of water are imbibed. The practical limitations of such a method are obvious. Perhaps the major contribution of the demonstration of the diuretic capacity of water is that it has shaken the former practice of limiting water intake of patients with congestive heart failure. There are areas in this country in which tap water contains so much sodium that it may, in a patient with heart disease, aggravate his edema[59], and this must be taken into account when the patient with edema is permitted free access to water.

PYRIMIDINE-DIONE OR AMINO-URACIL DIURETICS. Uracil drugs, which might be said to be related to the xanthines, exert a diuretic action and are presently being examined for utility as oral diuretics. A number of amino-uracil or pyrimidine-dione drugs have been examined and compared for diuretic activity in animals. Gilbert and Flack[130] found that they induced diuresis in man after oral administration. Kattus *et al.*[183] compared several of these with a number of xanthine compounds and found that, whereas the uracils were not as potent as emetics as the xanthines, neither were they as effective as diuretics. Some members of the amino-uracil group are also strongly emetic[161,340]. Kattus and Newman[181] found they acted by inhibiting the tubular reabsorption of sodium in the dog.

Aminometramide (Mictine). Kattus *et al.*[182] found one member of this group, aminometramide (Mictine) to be both a potent diuretic and significantly less emetic than others in the group. Bio-assay tests in man indicate useful diuretic potency by mouth[124]. Van Arman and Dettlebach[366] studied the pharmacologic action of aminometramide and found that it induced no effect on glomerular filtration rate or renal blood flow and, that it did not inhibit succinic dehydrogenase or carbonic anhydrase. On the other hand, injection directly into one renal artery produced diuresis in both kidneys. It was presumed, nevertheless, that the drug acts on the renal tubule. The practical value of this diuretic remains to be determined.

OSMOTIC DIURETICS. The use of osmotic diuretics, for example, urea, has declined with the advent of new, modern and more potent, and more dependable diuretics. Tarail *et al.*[358,359] found that when hypertonic glucose increased urine flow the sodium diuresis was small. Dicker[75] has recently demonstrated also that there is a reduced response to osmotic diuretics in puppies and newborn rats which may be related to a low glomerular filtration rate. These observations provide little incentive for a search for a new osmotic diuretic.

ALBUMIN. Concentrated serum albumin, especially the salt-poor form, seems to be a logical device for the patients who suffer from hypo-albuminemia or hypo-proteinemia. Patek *et al.*[268] report, however, that serum albumin concentrate was not followed by a sustained diuresis or disappearance of ascites in 3 patients with hypo-albuminemia. While plasma albumin and colloid osmotic pressure, plasma volume, glomerular filtration rate and renal blood flow all increased, diuresis was transient and there was no change in the rate of excretion of antidiuretic substance in the urine. Their studies suggest that low colloid osmotic pressure of the plasma is not the sole determining force in the ascites of cirrhosis and they postulate other factors, such as permeability of the portal vascular bed and disturbances in salt and water metabolism.

ISOCYTOSINES. Van Arman[365] examined a series of 34 isocytosine compounds (chemically related to both uracils and xanthines), one of which, SC–3858, was about 360 times as active a diuretic in the rat as urea but only weakly active in the dog. McKeever *et al.*[237] found that this compound increased sodium excretion in the rat. Trials in man by these observers showed it to be much less effective than mercurial diuretics. Further investigation of this group of drugs is necessary before a statement concerning potential clinical value can be made.

ALCOHOL. Strauss *et al.*[352] found that the alcohol diuresis, a common social observation in man, can be inhibited by pitressin. They suggested an action on the supra-optical hypophyseal mechanisms, one similar to that of water.

MISCELLANEOUS. The following are mentioned merely to indicate how broad is the search for agents which may prove to be useful as clinical diuretics. Waiteman and Brown[378] report a piperidine compound effective orally in the dog, Scholler *et al.*[311], an imidazole compound effective in animals. Belkin *et al.*[17] list 30 plants, not presently used for that purpose, which exert a diuretic action in man. There are no clinical data on any of these agents.

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SUMMARIO IN INTERLINGUA

(See page 542 for original article)

Le Responsa a Administrationes Parenteral e Oral de Rescinnamina in le Tractamento de Hypertension

1. Vinti-sex patientes hypertensive recipeva rescinnamina parenteral in doses ab 2,5 a 15 mg. Le evalutation del responsa de pression de sanguine e del effectos lateral fixava le optimal dose parenteral a 10 mg. Inter 20 patientes qui recipeva iste dose, 90 pro cento exhibiva un significative reduction del median pression arterial intra 5 horas post le administration del droga. Septanta pro cento deveniva normotensive.

2. Octanta-quatro (visitante) patientes hypertensive recipeva rescinnamina oral durante periodos de 2 a 4 menses o plus. Quaranta-septe pro cento del 84 patientes qui esseva tractate durante 2 menses exhibiva un significative reduction del pression al fin de iste periodo: 52 pro cento del patientes qui esseva tractate durante 4 menses o plus exhibiva un significative reduction del median pression arterial. Le responsa al droga non dependeva necessarimente del severitate del hypertension, sed le gruppo de patientes qui redeveniva normotensive includeva solmente 3 con initialmente sever grados de hypertension.

3. Rescinnamina, un pur alcaloide de *Rauwolfia serpentina*, se ha provate equal al previemente introducite alcaloide reserpina in su efficacia in le reduction del pression sanguinee. Su administration es accompaniate per plus o minus le mesme typos de effectos lateral como reserpina, sed le grado de certes de iste effectos lateral esseva minus alte.

PHYSIOLOGY

PROCEEDINGS OF

The Physiological Society of Philadelphia

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SEMINAR ON SYMPATHOMIMETIC AMINES

Introduction. G. B. KOELLE, M.D., PH.D. (Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania). Epinephrine was isolated from the adrenal medulla over half a century ago, and shortly thereafter T. C. Elliott proposed that it or a similar substance "sympathin," might function as the transmitting agent of the sympathetic nervous system. The important groundwork for our present knowledge of the subject was laid by Barger and Dale, Cannon, Loewi, and others. Some of the older concepts have since been modified. For example, Cannon's hypothesis of the unitary action of the sympatho-adrenal system has undergone revision through the recent studies of von Euler, Celander and others. It now appears that norepinephrine, liberated by the adrenergic nerves, is responsible for the minute-to-minute adjustments of the cardiovascular system, whereas the secretion of epinephrine by the adrenal medulla brings about the emergency responses to meet situations of "flight or fight." Among these responses, the metabolic actions of epinephrine are probably of considerable importance, since they are elicited by much lower doses than are required to affect smooth muscle.

Recent work has also confirmed some of the earlier conclusions which for many years were overlooked. There has been much discussion concerning the identity of the enzyme systems responsible for the destruction of epinephrine and norepinephrine. Although both agents are eventually metabolized nearly completely, it is likely that the termination of their immediate effects is brought about by their passage from extracellular to intracellular sites. This idea was proposed at the beginning of the century by Elliott, and has been mentioned more recently by several investigators, including Bacq, Dawes, and Blaschko. Recent work in our own laboratory, in collaboration with Dr. Kamijo, on the pharmacology of isonicotinic acid hydrazide and its isopropyl derivative has suggested the following picture: The structures of epinephrine and norepinephrine allow them to undergo three important reactions: 1) combination with the receptor groups of the effector cells, 2) passage through cell membranes and 3) attack by various enzymes. Drugs which can enter into some or all of these reactions can thus produce 1) sympathomimetic effects of adrenergic blockade, 2) potentiation of the effects of sympathomimetic amines, or 3) delay in their destruction.

Effect of Insulin Hypoglycemia on Epinephrine Concentration in Peripheral Plasma. R. A. MILLAR, M.B., CH.B., A. DET. VALK, M.D., AND H. L. PRICE, M.D. (Department of Anesthesiology, Hospital of the University of Pennsylvania). In the course of a general evaluation of the chemical method of Weil-Malherbe and Bone (Biochem. J., **51**,

311, 1952) for the estimation of epinephrine and norepinephrine in blood, the method, with certain modifications, has been used for the measurement of an epinephrine-like substance released during insulin hypoglycemia. Weil-Malherbe and Bone (Nature, **172**, 396, 1953) have claimed that insulin administration lowers the epinephrine concentration in peripheral blood, although this finding is at variance with a substantial body of pharmacological evidence.

Six studies carried out on 4 dogs demonstrated a rise in the estimated epinephrine level in peripheral venous plasma during hypoglycemia, from virtually zero to a mean of 2.14 μg./liter (range 0.51 to 4.11). The intravenous injection of glucose (5 to 6 gm.) was followed by a rapid fall in the estimated epinephrine level to a mean of 0.13 μg./liter. The response was further studied in 5 fasting subjects, in whom the rise in estimated epinephrine after insulin administration, was from zero to a mean of 1.22 μg/liter (range 0.37 to 2.30). During hypoglycemia, there was a consistent increase in systolic and a decrease in diastolic blood pressures, with an initial tachycardia which was usually not maintained. Ballistocardiographic tracings taken from 3 subjects, with the assistance of Dr. Isaac Starr, indicated an increase in stroke volume of 25 to 40%. Cardiovascular responses rapidly returned to basal levels following the intravenous infusion of glucose; the estimated epinephrine concentration in peripheral plasma fell to a mean of 0.06 μg./liter.

Arterial Responses to Epinephrine in the Denervated Bat's Wing. Mary P. Wiedeman, Ph.D. (Department of Physiology, Woman's Medical College of Pennsylvania.) The reactivity of arterial and arteriolar vessels to epinephrine was studied by direct observation in the wing membrane of the bat. Determinations of threshold concentrations were made of both intravenously injected and topically applied epinephrine. This was done in denervated wings and their contralateral normals.

When epinephrine was injected into the tail vein of a bat 2 weeks after section of the nerve to one wing, vessels in the wing constricted at a concentration of epinephrine that elicited no response in the contralateral normal. Thus, increased reactivity of denervated blood vessels in the subcutaneous areas of the bat wing was demonstrated. No difference in reactivity to topically applied epinephrine could be demonstrated between a vascular area denervated two weeks previously and a contralateral innervated area. This suggested that no alteration such as increased permeability of the cellular membrane or supersensitivity of the smooth muscle cell could account for increased responsiveness to intravenous epinephrine following denervation.

Denervation in the bat wing produces a marked and persistent relaxation of the blood vessels. An investigation was carried out to determine the relationship, if any, between the change in size of arterial vessels and increased responsiveness. It was found that the major artery to the wing and its immediate branches showed an increase in diameter of almost 30% over the contralateral normal vessels and this increase was still evident 25 days after denervation. Tests for responsiveness to injected epinephrine showed increased reactivity in 14 days, while topical epinephrine thresholds were unchanged. It was concluded that dilation of arteries after denervation does not affect their responsiveness to topical or injected epinephrine. This argues against the suggestion that increased responsiveness to epinephrine after

nerve section and regain of tone are concurrent.

The explanation for increased reactivity of vessels after denervation that fits most of the facts is increased permeability of vessel walls. This would allow more of the excitor agent per unit time to reach the effector cell. Experiments are now in progress to investigate this possibility.

The Role of Acetylcholine in Epinephrine-Hydrocarbon Arrhythmia. J. DIPALMA, M.D. (Hahnemann Medical College). The mechanism of the sensitization of the heart to epinephrine by a hydrocarbon has not been completely elucidated. This study was directed towards effects which the hydrocarbons might have on acetylcholine which in turn would alter the response of the heart to epinephrine. All the experiments were made on cats anesthetized with Dial-urethane. Anesthetic vapors were introduced in the tracheal cannula through a device which permitted measurement of the amount of drug inhaled per minute. Petroleum ether (mixed hydrocarbons) administered in a dose of 1 to 6 ml./min. caused loss of sinoatrial dominance. This shift of the pacemaker site was antagonized by acetylcholine. Diethyl ether in similar doses did not cause sinoatrial depression. Chloroform was similar in action to petroleum ether and was also antagonized by acetylcholine. In other experiments it was demonstrated that diethyl ether enhanced acetylcholine action on the heart in contrast to petroleum ether and chloroform which depressed it. Moreover, acetylcholine was capable of inhibiting the sinus node depressant effect of epinephrine. Finally it was demonstrated that acetylcholine could completely inhibit the ventricular arrhythmias brought on by epinephrine after hydrocarbon inhalation. Atropine even in large doses did not prevent this action of acetylcholine. The results were interpreted to indicate that the mechanism of epinephrine-hydrocarbon arrhythmias involved an inhibition of acetylcholine action on the heart rather than a sensitization to epinephrine.

Cardiac Effects of Methoxamine, with Special Reference to Intracoronary Injection. J. W. WEST AND D. M. AVIADO, JR., M.D. (Department of Pharmacology, University of Pennsylvania.) Development of techniques for catheterizing, under fluoroscopic guidance, the circumflex and anterior descending branches of the left coronary artery (West, Kobayashi and Schlesinger, unpublished) made possible, as one of its applications, study of direct drug actions upon the heart in intact dogs. Effects of intravenous and intracoronary injections of methoxamine were studied in dogs anesthetized with morphine and pentobarbital. Measurements were made of: a) Coronary blood flow obtained directly by collecting blood for a measured time, through a modified Morawitz cannula inserted fluoroscopically into the coronary sinus. b) ECG activity. c) Myocardial contractility, by a Walton Strain Gauge. d) Mean arterial blood pressure, by a damped mercury manometer or pulsatile pressure, by a capacitance manometer. e) Cardiac output, by the direct Fick method in dogs anesthetized with morphine and a combination anesthesia (Dial, urethane, pentobarbital). Data were obtained in several different animal preparations. In all preparations except those for cardiac output, the circumflex branch of the left coronary artery was catheterized fluoroscopically via one carotid for coronary arterial injections. Following control measurements, methoxamine given intravenously (0.1 mg./kg.) increased coronary flow approximately 10% with a rise in mean arterial blood pressure (approx. 40%) and concomitant decrease in heart

rate. Doses of 10 mcg./kg./min. intravenously decreased cardiac output and cardiac work by approximately 30% and 20% respectively. Total peripheral resistance increased approximately 90%. Intracoronary injections (0.001–0.4 mg./kg.) decreased coronary blood flow approximately 12%, with no immediate effect on blood pressure or heart rate and no increase in myocardial contractility. A tendency toward depression occurred with large doses, with essentially no immediate change in electrocardiographic pattern.

SUMMARIO IN INTERLINGUA

(See page 531 for original article)

Studios in re le Effecto de Superdosages de Combinationes de Pentylenetetrazol e Barbiturato in Voluntarios Human

1. Le ingestion de inter 1.300 e 2.000 mg de pentobarbital a natrium insimul con tres vices ille quantitate de pentylenetetrazol produceva nulle anesthesia e nulle sever depression del systema nervose central in voluntarios human. Del altere latere, le ingestion de inter 800 e 1.000 mg de pentobarbital a natrium sol resultava, in le majoritate del casos, in marcate depression del systema nervose central e in leve grados de anesthesia chirurgic.

2. Pentobarbital a sodium esseva absorbite ab le vias gastrointestinal plus rapidemente que fixe mixturas de pentobarbital a sodium con pentylenetetrazol.

3. Le tempo de disparition de pentobarbital a natrium ab le sanguine es le mesme in le duo gruppos, *i.e.* circa 1,5 pro cento del dose ingerite per hora.

4. Individuos ingerente secobarbital a natrium in doses de inter 1.300 e 1.500 mg insimul con tres vices ille quantitate de pentylenetetrazol monstrava nulle signo de marcate depression barbituratic. Le tempo de disparition ab le sanguine esseva circa 2,5 pro cento per hora.

5. Individuos ingerente phenobarbital a natrium in doses de inter 2.000 e 4.100 mg insimul con un e medie vices ille quantitate de pentylenetetrazol monstrava solmente sedation e esseva facile a eveliar. Le tempo de disparition ab le sanguine esseva in le caso de iste barbiturato approximativemente 0,7 pro cento per hora.

6. Multe individuos ingerente le combinationes de barbiturato con pentylenetetrazol reageva per vomito, demonstrante assi le disnarcotisation de lor mechanismo vomitive.

7. Le experimentos de controlo e etiam le revista del litteratura indica que pentylenetetrazol es un efficace contra-agente si illo es prendite insimul con doses comatose o possibilemente letal de un barbiturato.

8. In le combinationes e dosages supra-mentionate, pentylenetetrazol non produceva convulsiones. Ergo nos pote stipular que in humanos, sub le conditiones describite, pentylenetetrazol e barbituratos es mutualmente antagonistic.

BOOK REVIEWS AND NOTICES

THE SPINE: A RADIOLOGICAL TEXT AND ATLAS. BY BERNARD S. EPSTEIN, M.D., The Long Island Jewish Hospital, New Hyde Park, New York. Pp. 539; 721 ills. Philadelphia: Lea & Febiger, 1955. Price, $16.50.

DR. EPSTEIN has gathered a wealth of information on the spine in this one volume work. Disease processes of the spine have been well documented but this is a neat package which has gathered many loose ends by considering the spine as an entity. This is not only a radiologic text. Clinicians, neurologists, neurosurgeons, orthopedists and pediatricians will find this a valuable reference.

There is a fine discussion of the normal spine. The superb illustrations from Radiography and Clinical Photography (Eastman Kodak Company) have been included to demonstrate the anatomy of the vertebral column. The section on embryologic considerations aids in understanding the many anomalies of the spine. The author's experience makes itself evident in the discussion of the functional aspects of the spinal column. His views on asymmetric facets in the lower lumbar and lumbo-sacral region and narrowing of the lumbo-sacral interspace, for example, are basic and reflect long experience and thought on these subjects.

The spinal cord, and its covering have been well discussed in the various sections. This has of course included the various aspects of myelography.

Included in the contents are malformations of the spine, disease of congenital, endocrine or metabolic origin; inflammatory degenerative and noxious diseases; neoplasms; spinal traumatic changes; disease of the intervertebral discs; diseases of the hematopoietic, collagen and reticulo-endothelial systems; and a chapter on aortic aneurysms. H. W.

SELECTION OF ANESTHESIA. BY JOHN ADRIANI, M.D., Director, Department of Anesthesiology, Charity Hospital, New Orleans. Pp. 313; 30 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $6.50.

THIS book is recommended for teachers and pupils alike.

The fundamental pharmacology of anesthetic drugs, volatile agents, gases, and adjuvants so essential to a judicious evaluation of choice of anesthesia is presented at length.

The reader is continually impressed with the necessity for integrating a basic knowledge of pertinent pharmacology, a thorough understanding of the patient's surgical and nonsurgical disease, and anesthetic needs imposed by various surgical procedures.

The author has not added tedium by delineating anesthetic techniques.

The great value of epidural anesthesia in the armamentarium today, and especially for the poor-risk patient, is not emphasized.

Outstanding is the timely presentation of the physiology and pharmacology of the muscle relaxants, and the pitfalls inherent in the use of same.

Dr. Adriani's discussion of the causes of death in the operating room gives cause for soul searching. All anesthetists could profit from reading and re-reading this section.

Deserving of consideration is the author's discounting the importance of the vago-vagal reflex in cardiac arrest as an "overemphasized and convenient alibi for technical errors during anesthesia."

The comprehensive comparison of the physiologic differences of the pediatric and geriatric patient with regard to tolerance of anesthesia is excellent. E. C.

SWIFT AND CARROLL. A PSYCHOANALYTIC STUDY OF TWO LIVES. BY PHYLLIS GREENACRE, M.D. Pp. 306; 8 ills. New York: International Universities Press, 1955. Price, $5.00.

THIS book is a deep and scholarly psychological study of two well known writers, Jonathan Swift and Lewis Carroll. The author uses the psychoanalytic method in her appraisal and has linked the two because of the tendency they had to alter life in their own peculiar way for the entertainment of the reader. Both resorted to exaggerations in size, both coined new words, both made appealing nonsense, both drew heavily upon childish fantasy and both employed both satire and cruelty.

The family life and personality development of each is followed to cast some light upon his particular artistic creation. Very stimulating reading for the psychiatric specialist as well as for the sophisticated and curious physician-reader. O. E.

ARTHRITIS AND RADIOACTIVITY. By WADE V. LEWIS, B.Sc. Pp. 168. Boston: The Christopher Publishing House, 1955. Price, $2.50.

THE author, disclaiming "any medical knowledge whatsoever" gives an account of the effects of inhalation of radon as it occurs naturally in an abandoned mine in Boulder, Montana, on patients suffering from a variety of ailments, chiefly "arthritis." He is careful to make no claims himself, but rather presents a series (about 30 pages) of testimonials claiming relief from arthritis, rheumatic fever multiple sclerosis, asthma, sinusitis, dermatitis, infertility and impaired sexual function.

Although a short chapter is devoted to "What the Doctors Say," a careful reading of the entire book reveals a complete absence of informed rheumatologic opinion on the "before and after" status of the patients. Two doctors (names withheld) claim improvement after treatment in 3 cases of arthritis (presumably rheumatoid); one doctor states that "50% of my patients *claim* help or benefit" but withholds his own opinion. One doctor states that a patient's wrist, suffering from traumatic arthritis was improved.

This paucity of factual medical observation contrasts with the claims of over 30 patients of relief of pain and recession of joint manifestations and improved function which is stated to occur in "about 80% of cases."

The rest of the book deals with the known facts of radium disintegration and is repetitive in style. Chapter 12 deals with "Romance, Sex Life and Arthritis." Other chapters discuss hydrocortisone and give a hasty generalization as to the *modus operandi* of radon inhalation via the endocrine system. Full directions are given as to how to get to Boulder, Montana.

Charitably considered, this book may be thought of as an unwise excursion on the part of one trained in one branch of science into the unknown territory of another branch of science. J. L.

TUMOURS OF LYMPHOID TISSUE. By GEORGE LUMB, M.D., Westminster Medical School, London University. Pp. 204; 193 ills. London: E. & S. Livingstone, Ltd., 1954 (Williams & Wilkins Co., Baltimore, U. S. Agents). Price, $8.00.

THE material and conclusions which make up the bulk of this book are based on the study of 410 cases of malignant lymphoma at Westminster Hospital between 1940 and 1952. The opening chapters are on anatomy, physiology, history and classification and are brief and to the point. The author's classification is a simple one and but for slight differences in terminology, is the same as that most widely used in the United States. The next six chapters each deal with a specific lymphoma type. Statistics of incidence and of life expectancy drawn from the author's series are compared with those of the literature. The pathological and the differential diagnoses constitute the greater portion of each chapter and it is obvious that Dr. Lumb is drawing from a large personal experience. The greatest single section of the book is headed "Problems of Diagnosis" and for the pathologists, this is the most valuable portion. Here, the author defines the usual pitfalls, describes common conditions which mimic the malignant lymphomas and even gives some helpful suggestions in regard to technique. Finally, the book deals with therapy and states what one may expect to achieve.

The printing is beautifully done; the text is generously illustrated. Some of the magnifications are too small to be of much help, but by and large, this aspect of the book is above average.

The book should appeal to oncologists, pathologists, and to radiotherapists especially, but anyone handling cases of lymphoid tumors will profit by its reading. E. A.

KLINISCHE ELEKTROPATHOLOGIE. I. KRITISCHE SAMMLUNG ELEKTROPATHOLOGISCHER GUTACHTEN AUS INTERNER SICHT. II. DIE NEUROLOGIE DES ELEKTRISCHEN UNFALLS UND DES BLITZSCHLAGS. (Arbeit und Gesundheit, Heft 55.) By DR. MED. HABIL. S. KOEPPEN AND PROF. DR. F. PANSE. Pp. 424; 60 ills. Stuttgart: Georg Thieme Verlag, 1955 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $7.85.

IN the first part of this monograph Koeppen discusses the effects of electric injury upon internal organs, particularly the heart, the so-called angina pectoris electrica, possible relationships to hypertension, vegetative dystonia, angiopathies, emphysema, exophthalmic goiter and other endocrine disturbances. The changes in the central and peripheral nervous system induced by electric accidents and by lightning are outlined by Panse, who deals also briefly with electromagnetic waves and atomic energy. The contributions of the two authors were written independently so that considerable overlapping, for example, regarding the effects upon the spinal cord.

resulted. Numerous critically analyzed case histories, differential diagnostic considerations, excellent illustrations and a good bibliography add to the value of this monograph.

E. S.

Radiographic Atlas of Skeletal Development of the Knee. By S. Idell Pyle, Ph.D., and Normand L. Hoerr, Ph.D., M.D., Western Reserve University. Pp. 82; 29 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $4.25.

The late T. Wingate Todd, former professor of Anatomy of Western Reserve University and Director of the Brush Foundation, had initiated studies of human growth and development in 1926. He had assembled tentative developmental standards for the hand, elbow, shoulder, hip, knee and foot but had completed and published only one of them (Atlas of Skeletal Maturation-Hand). The first of the new series of atlases based upon the completed Brush Foundation collection of films is the Radiographic Atlas of Skeletal Development of the Hand and Wrist by Greulich and Pyle. The Radiographic Atlas of Skeletal Development of the knee is the second of this new series. It is another important contribution to the medical literature. The basic utilization of the atlas is in assessing the developmental level of a child's knee from Roentgen-ray films. It may also be used to distinguish between normal and abnormal knee joint contours. To use the plates properly one must digest the text. The wide range of developmental standards, among other things, will then be better appreciated. The authors hope the atlas will be of service in investigation of such problems as the effect of nutrition on growth and development, the effects of certain diseases on a child's symmetry of progress towards maturity. The atlas has been offered to clinicians for application to their problems, but not for the automatic solution of those problems.

H. W.

Induced Abortion on Psychiatric Ground: A Follow-up Study of 479 Women. By Martin Ekblad. Pp. 238. Copenhagen: Ejnar Munksgaard, 1955. Price, not given.

This book is a report of the findings of a psychiatrist working in the gynecological department of Sabbatsberg Hospital in Stockholm during 1949–1950 who observed the working out of the Swedish Abortion Act (June, 1938).

The Act provides four categories under which a legal abortion is sanctioned: (1) medical, (2) medical-social, (3) humanitarian and (4) eugenic indications. Medical indication exists where, on account of illness or physical defect in the woman, the advent of a child would entail serious danger to her life or health. Medical-social indication exists where because of "weakness" the advent of a child would entail danger. For example, the "worn-out" mother whose physical or mental forces would be impaired by the advent of the child and the care of the child. Humanitarian indications concern cases where the pregnancy occurs through coitus which implies a criminal act or a serious infringement of the woman's freedom to act. Eugenic indications deal with known transmissible conditions in one or both parents. The study is quite complete with two and a half years of follow-up including data on cases that were sometimes sterilized in connection with the abortion. Many interesting findings came to light.

As might be expected the risk of illegal abortion or suicide is greatest in those women who have been deserted by the male partner. A considerable number of the women studied became unintentionally pregnant again, frequently by the same man. Fourteen per cent had mild self-reproaches and 11% had serious self-reproaches. The author feels that legal abortion is only one of the many means of dealing with the complex problem of unwanted pregnancies. There is a wealth of interesting data and food for thought in this highly recommended study.

O. E.

Adrenal Function in Infants and Children. Report of 13th M & R Pediatric Research Conference under the Auspices of Department of Pediatrics, State University of New York Upstate Medical Center, Syracuse, November 3 and 4, 1954. Pp. 102; 26 ills. Columbus, Ohio: M & R Laboratories, 1955.

Participants in this Symposium included pediatricians, biochemists, anatomists, physiologists, and investigators in other disciplines. Pediatricians and endocrinologists will find presented much authoritative information on the biochemical, physiological and clinical aspects of the subject. Some of the diversified subjects covered include chromatographic studies of urinary steroids in infants and children, serum corticoid response to ACTH in infants, the origin of dehydroisoandrosterone, excretion of aldosterone in normal

children and children with nephrosis, plasma neutral 17-ketosteroids in pregnancy, and others. The adrenogenital syndrome is well covered. Certain aspects of steroid metabolism, the present status of therapy, genetic aspects and psychologic findings are given careful consideration. A. D.

INTRODUCTION TO CHEMICAL PHARMACOLOGY. By R. B. BARLOW, Yale University School of Medicine. Pp. 343; 53 ills. and numerous chemical formulae. London: Methuen and Co., Ltd.; New York: John Wiley & Sons, Inc., 1955. Price, $6.25.

DR. BARLOW's book is an outgrowth of a course in Chemical Pharmacology presented by Dr. H. R. Ing and Professor J. H. Burn for students in chemistry at Oxford. In his foreword Dr. Ing states that the book "attempts to instruct chemists on these difficult problems of drug action." A large, but concise, body of information is presented on the structure-activity relationships for those drugs acting on the central and peripheral nervous systems, at synapses, and on muscular organs. A nicely conceived, 24-page appendix introduces the chemist untrained in biology to the basic biological information. With the exception of a few minor biological and chemical errors or misprints, the book is a fine introduction to a limited field of medicinal chemistry for the chemist and a useful collection of structure-activity data for the pharmacologist. The author has not introduced new concepts of structure-activity relationships, but has weighed the current interpretations with sound judgment. S. E.

PROBLEMS OF CONSCIOUSNESS, Edited by HAROLD A. ABRAMSON, M.D., Assistant Clinical Professor of Physiology, Columbia University College of Physicians and Surgeons. Pp. 180; 10 ills. New York: Josiah Macy, Jr. Foundation, 1955. Price, $3.50.

THIS is an edited transcription of the fifth and last conference on "Problems of Consciousness," sponsored by the Josiah Macy, Jr. Foundation. It is divided into five sections. The first, "Three Dimensions of Emotion," sets the theme of the remainder, that ". . . emotion is simply a tag we put on behavior which is highly activated and which is at one end of the continuum." In the section on anxiety, consciousness is discussed as a summation of inborn thinking and feeling processes in relation to the environment. There is much discussion about the definition of consciousness. Emphasis is placed on its communicability and its integration of past, present, and future. The question of subjective and objective measurement is disputed and again related to a continuum. The sections on the role of the cerebral cortex in the development of consciousness and aesthetics largely continue the discussion.

Since the participants are speaking to those outside their own fields, they must utilize concrete illustrations of their ideas, but even with this, verbalization is difficult and makes understandable Dr. Fremont-Smith's remark at the last APA conference, that "misunderstanding is the commonest form of understanding."

The book has interest too, as a study in group interaction among leading scientists, and for the enjoyment of the many aphoristic comments of the members of different disciplines. O. E.

NEW BOOKS

Society and Medicine. Lectures to the Laity, No. 17. The New York Academy of Medicine. Edited by IAGO GALDSTON, M.D. Pp. 128. New York: International Universities Press, Inc., 1955. Price, $3.00.

THE New York Academy of Medicine is to be congratulated upon its program of lectures to the laity and upon the high standard of excellence which these lectures have set. The present volume, the seventeenth in the series, presents the following: Disease and Its Local Setting, by Sir James Spence, M.D.; The Biology of Ethics, by R. W. Gerard, M.D.; The Natural History of Neurotic Behavior, by Howard S. Liddell, Ph.D.; Environment and Heredity, by Theodore H. Ingalls, M.D.; Changing Concepts of Child Care, by Milton J. E. Senn, M.D., and Environment and Nutrition, by Russell M. Wilder, M.D. R. K.

L'Homéopathie. By PIERRE VANNIER, Former Chief of Clinic of the Paris Medical Faculty. Pp. 136. Paris: Presses Universitaires de France, 1955. Price, not given.

THIS small monograph is one of several hundred "What do I know?" paperbacks issued in France for popular reading. It describes the development and practice of homeopathy, based primarily on the work of Samuel Hahnemann. Despite homeopathy's untenable tenets of similitudes and tiny doses, Hahnemann's plea against indiscriminate drugging and insistence upon individualization of patients with medical treatment supported by dietetic and hygienic measures, constituted genuine contributions to medical thought. Present-day applications of this largely obsolete system of therapy are also mentioned. F. R.

Saddle Block Anesthesia. By Ray T. Parmley, M.D., Director, Department of Anesthesiology, St. Francis Hospital; Lecturer in Anesthesiology, University of Kansas School of Medicine. Pp. 58; 9 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $2.50.

This monograph was prepared after ten years of experience with saddle block for perineal and rectal surgery. The author is neither an ardent advocate nor a violent opponent of spinal anesthesia for obstetrics.

The text includes general considerations and uses of saddle block anesthesia describing the technique, premedication and uses and selection of doses of drugs.

The major portion of the book is devoted to the uses of saddle block in obstetrics with special emphasis on the time of inducing the block, precautions and indications for its use.

Anyone using saddle block anesthesia should read this excellent textbook. L. K.

The Josiah Macy, Jr. Foundation, 1930–1955: A Review of Activities. Pp. 174; 1 ill. New York: Josiah Macy, Jr. Foundation, 1955.

New Age Determinations by the Lead Method. By J. Laurence Kulp, George L. Bate, and Bruno J. Giletti, Ann. New York Acad. Sci., 60, Art. 3, pp. 509–520. Pp. 12. New York: New York Acad. Sci., 1954. Price, $.50.

Bioflavonoids and the Capillary. By Gustav J. Martin, and Albert Szent-Györgyi, *et al.* Ann. New York Acad. Sci., 61, Art. 3, pp. 637–736. Pp. 100; illustrated. New York: New York Acad. Sci., 1955. Price, $3.00.

Recent Advances in the Study of the Structure, Composition, and Growth of Mineralized Tissues. By Roy O. Greep, Albert E. Sobel, *et al.* Ann. New York Acad. Sci., 60, Art. 5, pp. 541–806. Pp. 266; illustrated. New York: New York Acad. Sci., 1955. Price, $4.00.

Molecular Events in Differentiation Related to Specificity of Cell Type. By H. Clark Dalton *et al.* Ann. New York Acad. Sci., 60, Art. 7, pp. 965–1160. Pp. 196; illustrated. New York: New York Acad. Sci., 1955. Price, $3.50.

Instrumentation. By Joseph Greenspan *et al.* Ann. New York Acad. Sci., 60, Art. 6, pp. 807–964. Pp. 158; illustrated. New New York: New York Acad. Sci., 1955. Price, $3.00.

Hydrocortisone, Its Newer Analogs and Aldosterone as Therapeutic Agents. By Joseph W. Jailer *et al.* Ann. New York Acad. Sci., 61, Art. 2, pp. 281–636. Pp. 356; illustrated. New York: New York Acad. Sci., 1955. Price, $4.50.

The Regulation of Hunger and Appetite. By Franklin Hollander *et al.* Ann. New York Acad. Sci., 63, Art. 1, pp. 1–144. Pp. 145; illustrated. New York: New York Acad. Sci., 1955. Price, $3.00.

Das Problem geopathogener Erscheinungen vom Standpunkt der Geophysik. By Doz. Dr. Volker Fritsch. Pp. 47; 21 ills. Munich: J. F. Lehmanns Verlag, 1955. Price, DM 6.

A General Theory of Association. By Robert Ginell. Ann. New York Acad. Sci., 60, Art. 5, pp. 521–540. Pp. 22. New York: New York Acad. Sci., 1955. Price, $.75.

Report of the Medical Research Council for the Year 1953–1954. Pp. 274. London: Her Majesty's Stationery Office, 1955. Price, 7s.6d.

Expert Committee on Midwifery Training. First Report. World Health Organization Technical Report Series No. 93. Pp. 21. Geneva: World Health Organization, 1955. Price, $.30.

Expert Committee on Biological Standardization. Eighth Report. World Health Organization Technical Report Series 96. Pp. 19. Geneva: World Health Organization, 1955. Price, $.30.

Chronicle of the World Health Organization, Vol. 9, No. 5, May, 1955. Pp. 20. Geneva: World Health Organization, 1955. Price, $.30.

NEW EDITIONS

Food Poisoning. By G. M. Dack, Ph.D.,M.D., Professor of Microbiology and Director, Food Research Institute, University of Chicago. 3rd ed. Pp. 251. Chicago: University of Chicago Press, 1956. Price, $6.00.

The manifold problems of food poisoning are a never-ending challenge to all practicing physicians. These problems may assume major proportions in institutions, military establishments and at times of major disaster. Therefore, the third edition of this book with its new material and its practical approach to the subject should have a wide appeal. R. K.

Medical Greek and Latin at a Glance. By Walter R. Agard, B. Litt. (Oxon), Professor of Classics, University of Wisconsin, and Herbert M. Howe, Ph.D., Associate Professor of Classics, University of Wisconsin. 3rd ed. Pp. 96. New York: Paul B. Hoeber, Inc., 1955. Price, $1.85.

This small volume presents in a concise, convenient form the most common Greek and Latin words whose derivatives are important in the study of medicine. The text is designed for undergraduate students who expect to enter medical schools, and has had a thorough trial in a terminology course at the University of Wisconsin. It should be helpful especially to pre-medical students who have had no formal training in Latin and Greek. C. Z.

Cardiolipin Antigens. By Mary C. Pangborn, Ph.D., J. O. Almeida, M.D., F. Maltaner, Ph.D., A. M. Silverstein, Ph.D., and W. R. Thompson, Ph.D. 2nd ed. Pp. 52. Geneva: World Health Organization, 1955. Price, $1.25.

This little monograph is devoted to methods of preparation of cardiolipin antigens along with chemical and serological control examinations. It includes an annex on introduction to applications and a complete bibliography on technical methods. It was prepared under the auspices of WHO which includes the setting up of biological standards as part of its technical activities. Although the preparation of cardiolipin antigens is too laborious for average laboratories, the monograph should be of great value to those engaged in this enterprise. J. K.

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